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AMITRAZ (BAAM): POSITION DOCUMENT 3

SPECIAL PESTICIDE REVIEW DIVISION
OFFICE OF PESTICIDE PROGRAMS
OFFICE OF TOXIC SUBSTANCES
U.S. ENVIRONMENTAL PROTECTION AGENCY

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U.S. ENVIRONMENTAL PROTECTION AGENCY

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Amitraz (BAAM): Position Document 3

I. Introduction

A. Background

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and its regulations require the Environmental Protection Agency (EPA) to review the risks and benefits of the uses of pesticides. On March 30, 1977, the Agency initiated this review for amitraz, an insecticide and miticide, with the issuance of a notice of rebuttable presumption against registration (RPAR) of pesticide products containing amitraz (42 FR 18299-302, April 6, 1977). Since that time, the Agency has received rebuttal comments and has conducted in-depth risk and benefit analyses. This Position Document (PD3) responds to the rebuttal comments, summarizes the risks and benefits of amitraz and recommends a regulatory option for each use.

This PD3 fully discusses the scope of the problem to be regulated, the process for selecting the alternative courses of action, and the rationale for the Agency's proposed final decision. It contains six parts. Part I is this introductory section. Part II is an evaluation of the potential risks of amitraz. It includes descriptions of the relevant laboratory data on risks, exposure data, and the Agency's present risk assessment. Part III is a discussion of the estimated economic benefits of amitraz and the limits of these benefits data. Part IV is a description of the range of the regulatory options for the reduction of risks and explains the basis of the Agency's selection of four alternative courses of action for each use of amitraz. Part V is an evaluation of the risks and benefits of amitraz on a use-by-use basis. It presents the beneficial and adverse impacts for each course of action. Finally, Part VI is a summary of the regulatory actions which the Agency proposes to take concerning the registration of pesticide products containing amitraz.

B. Applicable Sections of FIFRA

The Agency is considering the pending application for registration of amitraz, which is not currently registered for any end uses. Therefore, the applicable sections of FIFRA (7 U.S.C. 136 et seq.) are Sections 12(a)(1)(A) and 3(c)(5).

Section 12(a)(1)(A) prohibits the sale or distribution of pesticide products which are not registered by the Administrator. Section 3(C)(5) sets forth the grounds for approval of a registration.

Essentially, Section 3(c)(5) says that the Administrator will register a pesticide if it is efficacious, if its labeling is adequate, if it will work without causing unreasonable adverse effects and if when used in accordance with "widespread and commonly recognized practice" it will not cause unreasonable adverse effects.*/ Under Section 3(c)(5), the Administrator may in his discretion waive data requirements pertaining to efficacy and register a pesticide without determining whether it is efficacious.

In the case of amitraz, the Agency has presumed in the RPAR notice that an unreasonable adverse effect may occur. FIFRA offers several routes of action to the Administrator. First, he may classify the chemical for restricted use and impose use conditions which would reduce the risks enough to avoid unreasonable adverse effects [Section 3(d)(c)(1)(C)(ii)]. Second, he may conditionally register the pesticide for a short period of time and impose use conditions or data requirement's or both; he may do this only if doing so will not result in any unreasonable adverse effects and if other prerequisites for conditional registration are met [Section 3(c)(7)(C)]. Third, he may deny the registration and inform the applicant for registration of his determination and his reasons [Section 3(c)(6)]. These regulatory options are reviewed in detail in Parts IV, and VI.

C. The "RPAR" Process

The Agency has designed a process, known as the Rebuttable Presumption Against Registration (RPAR) process, to gather risk and benefit information about pesticides which appear to pose adverse health or environmental effects. This process allows an open, balanced decision and invites participation by all interested groups.

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*/ "Unreasonable adverse effects" is defined by Section 2(bb) of FIFRA as "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide."

This process is set forth in 40 CFR 162.11. These regulations describe various risk criteria, and provide that an RPAR shall arise if the Agency determines that any of these criteria has been met. Once a rebuttable presumption has arisen, registrants, applicants and interested persons may submit evidence in rebuttal or in support of the presumption. These people may also submit evidence on the economic, social and environmental benefits of any use of the pesticide. If the presumptions of risk are not rebutted, the benefits evidence submitted and that gathered by the Agency must be evaluated and considered with the risk information. Various risk reduction methods and their costs are then analyzed. Then it is determined whether the pesticide may be regulated so that its benefits outweigh its risks. If a balance between risks and benefits cannot be reached for a use, the registrations for that use must be cancelled or applications denied.

D. Chemical Background

1. Nomenclature

Amitraz is the common name for N'-(2,4-dimethylphenyl)-N-[[(2,4-dimethylphenyl)imino]methyl]-N-methylmethanimidamide. It is known in experimental use as U-36059, BTS 27419, RD 27419, Ent 27967, or JA-119. The formulated product for which registration with EPA is pending is called BAAM EC.

2. Chemistry

Technical grade amitraz is a white crystal with a melting point of 86° to 87° C. It is soluble in common organic solvents, but only slightly soluble in water. Its molecular weight is 293, and its molecular formula is $C_{19}H_{23}N_3$. Figure 1 shows its structural formula.

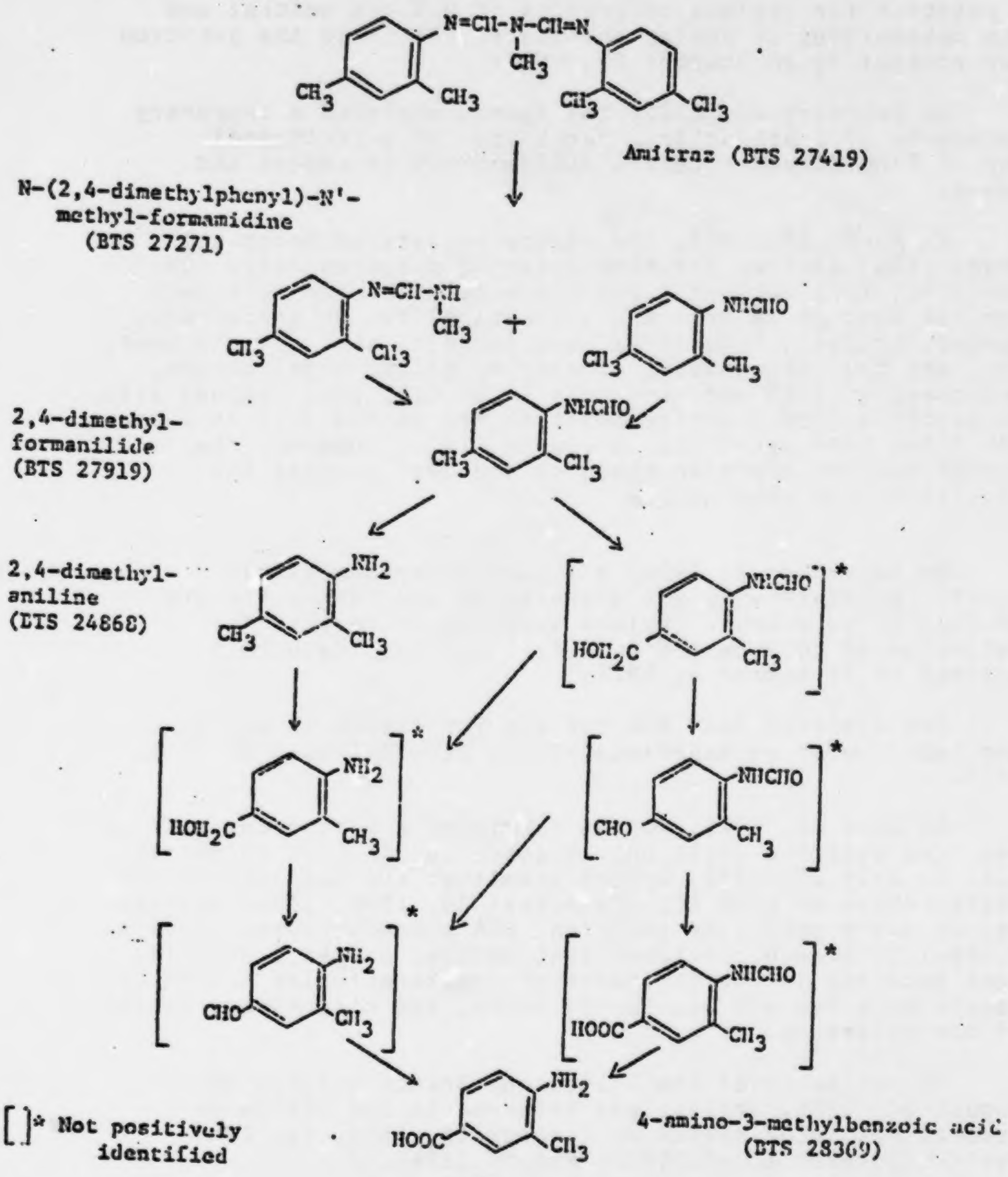
3. Metabolism

The metabolic pathway of amitraz in mammals has been proposed by the Boots Company through tests in dogs, rats, cows, and other animals (Upjohn 1976a). BTS 27271 and BTS 27919 have been identified as the major metabolites; BTS 24868 has been tentatively identified as an intermediate metabolite; and BTS 28369 has been found in urine (Upjohn 1976).

In apples and pears, amitraz (BTS 27468) degrades to BTS 27271 and BTS 27919 (Cox and Quick 1977). Under normal use conditions, very little of the parent compound is found after a few days and the major metabolite is BTS 27271.

Figure 1

THE PROPOSED PATHWAYS OF METABOLISM OF AMITRAZ IN ANIMALS


N=CH-N-CH=N
CH3
CH3
CH3
CH3
CH3
Amitraz (BTS 27419)
N-(2,4-dimethylphenyl)-N'-methyl-formamidine (BTS 27271)
N=CH-NH
CH3
+
NHCHO
2,4-dimethyl-formanilide (BTS 27919)
NHCHO
2,4-dimethyl-aniline (BTS 24868)
NH2
NHCHO
HOH2C
NH2
HOH2C
NHCHO
CHO
NH2
CHO
NHCHO
HOOC
NH2
HOOC
4-amino-3-methylbenzoic acid (BTS 28369)

[ ]* Not positively identified

E. Regulatory Actions Concerning Amitraz

1. Experimental Use, Registration and Tolerances

On October 7, 1974, the Upjohn Company submitted a petition for residue tolerances of 0.5 ppm amitraz and its metabolites on apples and pears. EPA filed the petition for processing on October 25, 1974.

On February 28, 1975, the Agency approved a temporary tolerance of 1 ppm amitraz for 1 year of experimental use of BAAM EC under permit #1023-EUP-34 on apples and pears.

On April 10, 1975, the Agency registered technical grade (93%) amitraz for manufacturing purposes only. On April 22, 1975, Upjohn submitted a petition for tolerance for residues of amitraz and its metabolites on grapefruit, lemons, oranges, tangerines, and tangelos at 1 ppm; in meat, fat, and meat by-products of cattle, goats, hogs, horses, and sheep at 0.05 ppm; and in milk at 0.01 ppm. Upjohn also submitted a food additive petition for citrus pulp at 3 ppm. EPA filed both petitions on June 5, 1975. However, the Agency has not approved these tolerances, pending the results of the RPAR review.

On September 2, 1975, a 1-year experimental use permit (#1023-EUP-35) was approved by the Agency for use of BAAM EC on citrus. Upjohn submitted a request for extension of this permit on July 7, 1976. The permit expired on September 2, 1976.

EPA approved BAAM 50W for use for 1 year on apples and pears under an experimental use permit issued April 5, 1976.

On June 22, 1976, Upjohn submitted a pesticide petition and food additive petition, as described in Part tolerance I.B. On July 23, 1976, Upjohn submitted its application for registration of BAAM EC. On August 30, 1976, after reviewing Upjohn's pesticide petition, EPA's Registration Division Toxicology Branch concluded that amitraz caused a significant increase in the incidence of lymphoreticular tumors in female mice fed 400 ppm for 80 weeks, and recommended denial of the tolerance.

On the basis of the Toxicology Branch conclusions of August 30, 1976, amitraz was referred to the Office of Special Pesticide Review on October 15, 1976, for RPAR review (Burnett et al. 1976; Rogoff 1976).

2. Specific Exemptions

In February, 1977, the Washington State and Oregon Departments of Agriculture applied for specific exemptions to use amitraz to control pear psylla on pears. In Washington, amitraz would be applied from one to three times by air blast sprayers at 1.25 to 2.0 lbs. active ingredient (a.i.) per acre; the application period would begin on May 1 and end on September 30, 1977; a maximum of 100,000 lbs. of amitraz would be used. Oregon's request covered the same period of time, but asked for one to three applications of 1.5 lbs. a.i. per acre on 23,500 acres (not to exceed 105,750 lbs. a.i.).

On March 24, 1977, the Agency granted these specific exemptions pursuant to Section 18 of FIFRA and 40 CFR 166.1. Some of the conditions for the use of amitraz (BAAM) were:

--The dosage rate would be 1.0-1.5 lbs. a.i. per acre,

--applications would only be made where other pesticides were not proving effective against pear psylla in a sound integrated pest management (IPM) program,

--there would be a pre-harvest interval of at least 7 days,

--there would be a 3 ppm amitraz residue limit in or on harvested pears, and

--applicators would have to wear protective clothing and respirators.

On March 30, 1978, the Agency approved specific exemptions to Washington, Utah, Oregon, Michigan, New York and Pennsylvania to use amitraz to control pear psylla. The conditions of use were similar to the 1977 exemptions.

3. Issuance of the RPAR

On March 30, 1977, the Agency's Office of Pesticide Programs (OPP) issued a notice of RPAR on amitraz (42 FR 18299-392, April 6, 1977) on the basis that amitraz met the risk criterion for oncogenic effects [40 CFR 162.11(a)(3)(ii) (A)] That notice was supported by Position Document (PD) 1 on Amitraz, which described the physical and chemical characteristics of amitraz, and the toxicological test results then available about it.

II. Risk Analysis

The Agency's Interim Procedures and Guidelines for Health Risk and Economic Impact Assessment of Suspected Carcinogens ("Interim Cancer Guidelines") specify that two decisions must be made about a potential carcinogen (41 FR 21401-21405, May 25, 1976). The first is whether a particular substance is a cancer risk and the second is what regulatory action, if any, should be taken to reduce that risk. This section deals with the first decision--whether amitraz poses a cancer risk.

The Interim Cancer Guidelines state, "a substance will be considered a presumptive cancer risk when it causes a statistically significant excess incidence of benign or malignant tumors in humans or animals." In its Preliminary Review of Oncogenicity of Amitraz (BAAM) (March 4, 1977) the CAG found that a statistically significant excess incidence of tumors occurred in a Boots Company mouse study of amitraz and in a National Cancer Institute (NCI) study of 2,4-dimethylaniline, a metabolite of amitraz. On the basis of these findings, the Agency issued a RPAR.

After the RPAR, the Agency initiated a detailed risk assessment in accordance with the Interim Cancer Guidelines. In the preamble to these guidelines, the Administrator stated that it is necessary to consider evidence for carcinogenicity as a "warning signal," the strength of which depends on the quality and scope of the data, the nature of the toxicological response and the potential impact on human health. Accordingly, the Agency's risk assessment addresses these important topics. This risk analysis is divided into four parts: Section A evaluates the rebuttal comments; Section B discusses the quality and scope of available data, and describes the toxicological responses; Section C estimates human exposure; and Section D estimates the potential risk from amitraz to humans.

A. Evaluation of Rebuttal Submissions

In its RPAR, the Agency reviewed several oncogenic and mutagenic tests submitted by the Upjohn Company. In a carcinogenic bioassay of mice, the "Boots Mouse Study", the Agency observed the induction of lung tumors and lymphoreticular (LR) tumors in female CFLP mice fed 400 ppm technical grade amitraz *ad libitum* in the diet for 80 weeks (Burnett *et al*. 1976). This finding met the RPAR criterion for a presumption of oncogenic risk.

During the RPAR comment period, the only rebuttal relevant to the presumption of risk was jointly submitted by the Upjohn Company and the Boots Company, Ltd. This rebuttal (the "Boots-Upjohn rebuttal") addressed nearly every statement made by the Agency in its RPAR Position Document 1, and in two EPA Carcinogen Assessment Group (CAG) reports.

The Agency has reviewed the Boots-Upjohn rebuttal submission and has concluded that: first, the Agency erred in its previous count of lung tumors in female CFLP mice; second, the rebuttal arguments did not change the Agency's conclusion that amitraz induced LR tumors in female CFLP mice; and third, 2,4-dimethylaniline, a metabolite of amitraz in mammals, induces a positive oncogenic response in mice and a positive mutagenic response in one bacterial strain. Each of these findings will now be developed by stating the Agency's position in the RPAR, the Boots-Upjohn rebuttal to that position, and the Agency's present position.

1. Lung tumors in Female CFLP Mice

In the RPAR, the Agency concluded that "the dose response relationship for lung lesions in female mice, whose sample sizes were corrected for survival, shows a significantly increasing linear trend." This finding had been made by the CAG in its "Preliminary Review of BAAM" (CAG, 1977b). In that report, the CAG had identified the lung lesions as hyperplasia, adenomas, and carcinomas. After correcting tumor counts for survival (i.e., eliminating animals with tumors that had died before the first detection of lung hyperplasia), the CAG had found the incidences of these tumors combined to be 0.26, 0.48, 0.34 and 0.55 in the control, low, middle and high-dose groups, respectively. The CAG had then evaluated the relationship between these tumor incidences and amitraz dosage, and determined that it was statistically significant ($p<0.05$).

The Boots-Upjohn rebuttal made three points to refute these findings. First, the rebuttal showed that the CAG's tabulation of lung tumor data contained several counting errors. Second, in correcting the data for survival, the CAG had miscalculated the lung tumor incidences. These should have been 0.24, 0.34, 0.28 and 0.38 in the control, low, middle and high-dose females, respectively; and not 0.26, 0.48, 0.34 and 0.55, as reported by the CAG. Further, when correctly counted, these values show no significant linear trend relationship between number of tumors and dose

($p>0.20$). Third, Boots-Upjohn asserted that the first female with a lung tumor died at 55 weeks and not at 73 weeks, as stated by the CAG in their correction for survival. From this point of reference, the incidences of lung tumors are 0.22, 0.36, 0.23 and 0.38 in the four female dosage groups. With these tumor incidences there is no apparent linear trend between dose and lung tumor response.

The CAG has agreed with these rebuttal arguments about lung tumors in female CFLP mice (Albert 1978a). Thus, the Agency finds that its RPAR presumption on lung tumors has been successfully rebutted.

2. Lymphoreticular (LR) Tumors in Female CFLP Mice

In the RPAR the Agency had considered three issues about the incidence of LR tumors in the female mice of the Boots Mouse Study: first, the statistics of the tumor incidences; second, the possibility that the LR tumors arose as a non-specific response to several factors in combination with amitraz; and third, the potential for viral induction of LR tumors.

a. Statistical Analysis

The Agency made two statistical conclusions in the RPAR. The first was that "the dose-response relationship for lymphoreticular (LR) tumors in female mice shows a significantly increasing trend ($p<0.02$)." The second was that "the incidences of LR tumors in the high dose (400 ppm) and control (0 ppm) female mice are 0.49 and 0.23, respectively, and are significantly different from each other ($p<0.03$)." The Agency noted that prior to its RPAR review of amitraz, the Boots Study authors, a Boots' consultant, and the Upjohn Company had all agreed that there was a statistically significant excess incidence of LR tumors in female mice fed the high dose of amitraz.

In their rebuttal, Boots-Upjohn confirmed their agreement with the Agency's second conclusion, but disagreed with the first conclusion, stating "any evidence for a dose response in treated females is weak, and does not attain significance until taken in conjunction with the result at 400 ppm..." To support this thesis, several points were made. First, it was suggested that the "nearly identical" LR tumor incidences of 0.32 and 0.34 in females receiving the low and middle doses of amitraz "argues strongly" against the CAG finding of dose-response. Second, it was suggested that the linear log-trend analysis used by the CAG "cannot be justified" because of a lack of information on dose-response curves of chemical carcinogens; even so, assuming a linear trend "may be the most convenient approximation." Further, when log-trend analysis is applied to the control, low-dose, and middle-dose female LR tumor incidences, there is no significant slope ($p = 0.25$). Thus, the Boots-Upjohn rebuttal concluded that it was the high dose (400 ppm) level alone which accounted for the statistical significance of the linear trend and that "to assert a linear trend, is...essentially repetitious and possibly misleading..."

The CAG has agreed that the two tests cited in the RPAR notice are not independent of each other; a relatively large response at the highest dose could make both tests become statistically significant. However, the trend test measures an aspect of tumor incidence data which is not tested when any one dose is compared to controls; this aspect is whether there is a tendency for the higher tumor incidences to be associated with the higher dose groups. As applied to the Boots Mouse Study data, the positive linear trend test is important because it emphasizes that the statistically significant excess incidence of LR tumors occurred in the highest dose group, rather than in one of the intermediate dose groups. This is consistent with the hypothesis that the effect is related to the amitraz concentration (Albert 1978c).

b. LR Tumors as a Non-Specific Response to Factors in Combination with Amitraz

The authors of the Boots Mouse Study postulated that the LR tumors in the high-dose female mice could have arisen from the combination of several factors and the diet of amitraz. Two consultants to the Boots Company generally supported this (Roe 1976; Vesselinovitch 1976).

(i) Mouse Strain

Both a consultant to Boots and one of the authors of the mouse study once suggested that the CFLP mouse is quite variable in its rate of spontaneous tumor formation; they have further suggested that this genetic characteristic may have contributed to the excess LR tumors in the high-dose female mice (Roe 1976, Turnbull 1976).

In the RPAR, the Agency had examined the spontaneous tumor rates in CFLP mice and found that "the historical incidence of LR tumors [in control mice] in the present

Boots study falls within the normal range of the incidences in historical studies." Consequently, it was concluded that it was highly unlikely that the LR tumors in the high-dose female mice arose spontaneously.

Boots-Upjohn have contended in their rebuttal that with the "very variable" background of the CFLP mouse "it is difficult to draw any definite conclusions as to the toxicological significance of the observed tumor incidence." To support this statement, Boots-Upjohn indicated that the incidence of LR tumors in 400 ppm-dosed females was twofold that of the contemporary control females (i.e., 49% compared to 24%), whereas female CFLP mice historically show a threefold variation of spontaneous LR tumors (10%-31%). They also stated that this incidence of LR tumors in CFLP mice is "notably more variable" than in the strains now preferred by scientists for cancer research.

In response to these statements, the CAG has acknowledged the variability of the LR tumor incidences in untreated CFLP mice (Albert 1978a). For the ten groups of untreated female mice (i.e., the historical controls), the spontaneous LR tumor incidences ranged from 0.10 to 0.31, with a mean incidence of 0.19. For males, the range was 0.02 to 0.27 and the mean was 0.13. Nevertheless, the tumorigenic response is always superimposed on the spontaneous occurrence. In the case of the high-dose females in the Boots Study, the LR tumor incidence was 0.48. Clearly, this falls outside the range of the historical controls. It is also significantly different from the matched controls (0.23) and the mean of the historical controls (0.19). Consequently, the CAG considered that the statistically significant LR tumor incidences in the high dose females was associated with the effect of amitraz (Albert 1978a).

(ii) Food Intake

The Boots Mouse Study authors suggested that overfeeding might be a contributory factor to the formation of LR tumors in the high-dose female mice. A study by Roe and Tucker (1974) was cited as evidence that an increased incidence of LR tumors is associated with overfeeding. However, the Boots Mouse Study authors also noted, "the level of food intake is unlikely to be the sole explanation for the higher incidence of lymphoreticular tumours in only been estimated, "because no account was taken of spillage which was widely variable in extent, especially between cages of females in each dosage group."

After examining the "overfeeding" hypothesis, the Agency had asserted in the RPAR that the incidence of tumors is related to bodyweight rather than the amount of food consumed; the Agency therefore found that Boots' food intake argument was unsupported.

In rebuttal Boots-Upjohn restated their conclusion: "...the possibility cannot be precluded that the nutritional status of the amitraz-treated females contributed to the pathogenesis of the LR tumors in these animals." They pointed out that the females at the high dose (400 ppm) ate more food relative to bodyweight than did high-dose males. Further, they cited a recent review by Clayson (1975), which holds that the yield of many tumor types depends significantly on the caloric value of the diet or on body weight of the animals. Boots-Upjohn concluded that the LR tumors in the high-dose female mice were possibly due to the increased caloric intake of these mice.

The CAG has noted that Clayson went on to say that the actual number of calories is "not necessarily significant" (Albert 1978c). Rather, bodyweight may be the determining factor in the development of tumors. Clayson, in turn, cited Tannenbaum and Silverstone as saying, "the relevant restriction was probably mediated through its effect on bodyweight." In other words, if two animals maintain the same bodyweight, but one consumes more calories, there should be no difference in their spontaneous tumor rates. At the termination of the Boots study, the females that had ingested 400 ppm amitraz had gained 18% less weight, on the average, than did control mice. Their average food consumption (g/100 g bodyweight), however, was 12.2% higher than that of the controls. Boots-Upjohn attributed the LR tumors in the high-dose females to the fact that they consumed more calories than did the controls. However, if tumor incidence is dependent on bodyweight, fewer tumors would be expected in the 400 ppm females than in the controls, since the weight of the high-dose females was less (Albert 1978c).

Because of the uncertainty over whether decreases of tumor incidence are due to caloric restriction or depressed growth of body weight, no clear case can be made that dietary factors were related to the excess LR tumor incidence in the high dose female mice. The CAG, therefore, concluded that the LR tumor incidence was linked to the exposure to amitraz and not to the caloric value of the diet or body weight (Albert 1978c).

c. Viral Induction of LR Tumors

The RPAR stated that the Agency had found no physical or statistical evidence of a vertical or horizontal viral spread which could be associated with the incidence of LR tumors in female mice. This conclusion was based on the CAG's detailed review (Albert 1977) of an Upjohn Company report (Kakuk 1976) that had proposed that an LR tumor-inducing virus had spread among the high and middle-doses females.

The Boots-Upjohn rebuttal made several points to support their previous position. First, they reiterated, "there is clear evidence that mice commonly carry a virus that may be expressed as LR tumors" (McKissick *et al*. 1970). Second, they claimed that they had found "virus-like particles" in the affected tissues of some of the treated mice (Robinson 1977). Third, they reexamined the statistical analyses performed by the CAG and explained that these analyses were "highly suggestive ($p = 0.058$) of some intercurrent viral infection transmitted between cage mates..." Finally, they suggested that the accidental administration of paraformaldehyde (mixed with the amitraz in the last 10 to 14 weeks of the study) may have acted with the viral spread to contribute to the LR tumors in the high-dose female mice.

In response to the first two points, the CAG believes that, although there are examples of viruses which cause tumors, in this particular case Boots-Upjohn did not provide physical evidence that a virus caused the LR tumors in the high-dose female mice (Albert 1978a).

On the third point, the CAG agrees with Boots-Upjohn that the LR tumor rates in the lower-left and lower-right cage quadrants differ at $p = 0.051$ (x^2 test), $p = 0.058$ (Fisher's exact test) and $p = 0.082$ (x^2 test plus Yates correction for continuity). While the CAG has acknowledged that the difference between the tumor rates in the two quadrants is nearly significant at $p=0.05$, this difference is not large enough to support Boots-Upjohn's hypothesis of viral spread. Since Boots-Upjohn provided the Agency with no physical evidence of viruses to support their contention, the CAG has concluded that the hypothesis of a viral etiology in the induction of LR tumors was not clearly established (Albert 1978c).

Finally, in response to the Boots-Upjohn concern over the paraformaldehyde contamination of the amitraz-feed mixture, the CAG has agreed that this incident somewhat confounds the test results. However, the CAG has concluded that the relation between the presence of paraformaldehyde and LR tumors remains completely speculative for three reasons: first, 10 to 14 weeks is too short for a carcinogen to act unless it is extremely potent; second, neither paraformaldehyde or formaldehyde are known to be carcinogenic; and third, there are no data for structurally similar compounds to indicate paraformaldehyde is carcinogenic (Albert 1978c).

3. Effects of a Metabolite 2,4-dimethylaniline

Data submitted by the Upjohn Company in support of the registration of amitraz stated that 2,4-dimethylaniline was tentatively detected in dogs' stomachs shortly after the dogs had ingested amitraz (Upjohn, 1976).

As noted in the RPAR, the Agency had reviewed a National Cancer Institute (NCI) oncogenic bioassay of 2,4-dimethylaniline in mice and rats; the RPAR found an excess incidence of sarcomas in treated female mice and of malignancies in treated male rats, when the treated animals were compared to their respective matched control groups.

In rebuttal, Boots-Upjohn asserted that the CAG had compared the frequency of malignant tumors in treated mice to the frequency of those tumors in the wrong control group. Further Boots-Upjohn contended that the tumor incidences of the six control groups should have been pooled and then compared to the incidences of the treated animals. Using this approach, Boots-Upjohn found that the incidences of these tumor types in treated mice did not significantly differ from those in the pooled controls.

Boots-Upjohn stated about the rats that 36% of the matched control animals and 12% of the treated animals were not examined. They suggested pooling the six control groups to make a "meaningful comparison" to the treated animals. With this method they found no differences in the number of malignant tumors in treated and control rats (8/44 vs. 12/111).

In response to the comments on mice, the CAG reviewed a final draft from NCI summarizing the results of this same oncogenic study of 2,4-dimethylaniline. In comparing the incidence of pulmonary tumors in female mice treated at the high dose (11/19) to the incidence of those tumors in the matched controls (5/22), the author reported a statistically significant difference ($p<.025$) (Weisburger, 1978). The CAG has concurred with these findings (Albert 1978c).

Regarding Boots-Upjohn's rebuttal comments on the rats, the CAG has acknowledged that an inadequate number of matched control rats were examined, and that the statistically significant malignant tumor incidence is not valid (Albert 1978e). Further, the CAG believes that the six control groups should not be grouped, since they were not all initiated at the same time.

Because Boots-Upjohn has acknowledged in its rebuttal that 2,4-dimthylaniline is a metabolite in mammals and because of the finding by NCI that this metabolite induced pulmonary tumors in female mice, the Agency also concludes that amitraz may pose an oncogenic hazard to man (Albert 1978a).

In addition, the Agency has reviewed mutagenicity data submitted by Boots-Upjohn on 2,4-dimethylaniline. In the TA 100 strain of *Salmonella typhimurium* (Ames Test), this compound gave positive results in three replicate tests. The CAG has found the test procedures and their results to be accurate and valid (Albert 1978a). The Agency concludes, that although these test results are not sufficient to meet the RPAR criterion for mutagenicity, they corroborate the conclusion that amitraz may pose an oncogenic hazard to man.

B. Qualitative Assessment of Risk Data

To provide a judgment on the "weight" or meaning of the available evidence, the Agency has evaluated the quality of the relevant toxicological studies of amitraz and of 2,4-dimethylaniline. The Agency has also assessed the nature and extent of the toxicological responses observed in these studies.

1. Studies on Amitraz

a. Boots Mouse Study

The CAG has concluded that the Boots study has irregularities which may undermine its reliability: the accidental dosing of animals with paraformaldehyde[*/] in the last 14 weeks of the study; a nearly significant difference between the number of tumor-bearing females in one quadrant of cages as compared to another quadrant; and the sub-optimal length of the study (80 weeks instead of 104 weeks). These factors led the CAG to conclude that the Boots Mouse Study was "less than ideal" and that another mouse oncogenic bioassay should be performed (Albert 1978e).

The pathological diagnoses of the female mouse LR tumors varied significantly. Seven pathologists reviewed the slides or gave opinions: the Boots Study authors (Burnett et al. 1976); Dr. Francis J.C. Roe, a consultant to Boots who reviewed selected slides; Dr. Stanley D. Vesselinovitch, a consultant to Boots who did not review the slides, but submitted an opinion; Dr. Thomas Kakuk, an Upjohn Company pathologist who reviewed some of the slides; Dr. Melvin Reuber, a consultant to the CAG who assessed all the slides; Dr. I.N. Dubin, a consultant to the CAG who reviewed most of the slides; and Dr. Squire, a consultant to the CAG who reviewed only selected slides independently of and then together with Dr. Dubin. Although there were four different opinions from the Boots and Upjohn Companies, these were apparently consolidated into a unanimous opinion in the Boots-Upjohn rebuttal submission (Upjohn Co. 1977).

The Boots-Upjohn LR tumor counts in the highest dose and control female mice, along with the three opinions obtained by the CAG consultants, are presented in Table 1. Because of the difficulty in defining the exact demarcation between lymphoreticular tumors and their precursor lesions, there were some differences among the pathologists in observed LR tumor incidences (Albert 1978e). The Boots-Upjohn pathologists found a tumor incidence that was significant at $p=0.0078$; Dr. Reuber, $p=0.002$; Dr. Dubin, $p=0.173$; and Drs. Dubin and Squire together, $p=0.024$. It should be noted that the Dubin-Squire opinion resulted thus:

[*/] Although paraformaldehyde is not known to be a mutagen or carcinogen, its monomer, formaldehyde, is a mutagen (Albert 1978e).

Dr. Squire reviewed only the slides for animals (28) in which Dr. Dubin did not observe LR tumors and in which Boots-Upjohn did see tumors. Dr. Squire concluded that only about half(12) of the animals in question had LR tumors. Then Dr. Dubin and Dr. Squire looked at these particular slides together. They reevaluated their criteria for judging LR tumors. As a result, Dr. Dubin classified as lymphomas (LR tumors) seven lesions which he had not so previously classified in the high dose females. Together, Drs. Dubin and Squire concluded that seven of the twelve animals in question had tumors. Adding these tumors to Dr. Dubin's original review (see "Dubin" column), which was not statistically significant, created a diagnosis that was statistically significant (see "Dubin and Squire" column).

One of the CAG consultants, Dr. Reuber, observed a statistically significant incidence of LR tumors in the highest dose (400 ppm) male mice (p=0.024). Neither Dr. Dubin or Boots-Upjohn found a significant result.

Table 1. Pathological Diagnoses of Lymphoreticular Tumors in Female Mice

	Boots-Upjohn	Reuber	Dubin	Dubin and Squire
Controls	10/43 (21%)	10/43 (23%)	6/43 (14%)	7/43 (16%)
400 ppm amitraz	23/47 (49%)	29/47 (62%)	11/46 (24%)	17/46 (37%)
Fisher exact test "p" value	0.007	0.002	0.173	0.024

Finally, Dr. Reuber also observed a statistically significant incidence of malignant liver tumors (combined hepatocella carcinomas and hemangiosarcomas) in all amitraz-dosed male mice as compared to the controls (Albert 1978e). However, this finding was not supported by the slide analyses of Boots-Upjohn or of Dr. Dubin. The CAG chose not to sum the two different histological types of maliginant liver neoplasms to determine significance. Instead, they combined benign adenomas and carcinomas, since the former is recognized as a precursor of the latter. There was no significant effect of amitraz at any dose level (Albert, 1978e).

b. Boots Rat Study -- The CAG found that this study was valid and that there was no statistically significant excess incidence of any tumor type in males or females (Albert 1977).

c. Boots-Upjohn Mutagenicity Tests -- While the registrant submitted the results of several mutagenicity tests, the CAG found the data insufficient for defining amitraz as a mutagen or non-mutagen, because of deficiencies in the protocols (Albert 1978e). The authors of the study had reported that amitraz caused no response in those tests.

2. Studies on 2,4-dimethylaniline

a. National Cancer Institute Mouse and Rat Oncogenic Bioassay

The CAG has reviewed an NCI oncogenic bioassay on 2,4-dimethylaniline; they agreed with the author, Dr. Elizabeth Weisburger, that a significant excess incidence of pulmonary tumors occurred in the high-dose female mice as compared to the matched controls (Albert 1978c). No significant tumor rates were observed in the low-dose female mice, in any of the male mice, or in any of the treated male rats, as compared to the control animals. The CAG believes that the protocols of these studies were acceptable. However, the contractor for NCI who performed the tests noted that weight gain and survival in treated mice and rats were not altered, which raised the question as to whether the maximum tolerated doses had been administered.

b. Mutagenic Tests by the Boots and Upjohn Companies

The CAG also reviewed mutagenic test data submitted by the registrant and found a positive mutagenic response in one strain (TA 100) of bacteria (*S. typhimurium*). The data in three replicate dose-response curves appeared to be accurate and valid (Albert 1978a). No mutagenic response was seen in the other four strains of bacteria tested.

c. Metabolism Studies

The role of 2,4-dimethylaniline in the metabolism of amitraz in mammals is uncertain. According to the registrant, there are two likely routes of metabolism (see Figure 1). Of the possible metabolites in the one route, only 2,4-dicompounds predicted in the other route have been identified. The proportion of ingested amitraz which may form 2,4-dimethylaniline is unknown; consequently, the CAG could not perform a quantitative risk assessment for this metabolite (Albert 1978e).

3. Conclusions

EPA's Interim Cancer Guidelines describe the weight that should be given to various kinds of risk evidence. The "best" evidence is provided through epidemiological studies of humans confirmed by animal tests. "Substantial" evidence comes from animal tests showing excess incidences of malignant tumors, including benign tumors that are recognized as early stages of malignant tumors. "Suggestive" evidence may consist of non-life-shortening benign tumors, mutagenicity tests, initiation-promotion skin tests and ancillary information.

In the case of amitraz, there are no epidemiological data available. Of the animal oncogenicity tests conducted on this compound on both sexes of two species at three doses (plus control), an excess incidence of one tumor type (lymphoreticular) was seen by several pathologists in one sex (female) of one species (mouse) at one dose (400 ppm). There are questions about the protocols and results of the mouse test, and so another test has been recommended by the CAG. Further, the mutagenicity tests performed on amitraz were difficult for the CAG to interpret due to deficiencies in the protocols. Even so, additional evidence to support the possibility of risk is the NCI study of 2,4-dimethylaniline, which demonstrated an oncogenic effect in female mice at the highest dose, and a positive mutagenic response in the Ames test.

In summary, the reliability of the Boots mouse study was questioned, although a few positive effects were observed. Also, 2,4-dimethylaniline gave one positive oncogenic response in animals and a single mutagenic response in bacteria. The Agency concludes that there is weakly positive evidence for the oncogenicity of amitraz.

B. Human Exposure to Amitraz

From information provided by the U.S. Department of Agriculture, State Extension Service personnel, the Boots-Upjohn rebuttal, and other sources, the Agency has identified human populations exposed to amitraz, the route of their exposure, and the extent of their exposure.

1. Dietary Exposure

The Agency has estimated the potential dietary intake of amitraz by the U.S. population from treated fresh and processed pears and apples (Garner 1978; Mittelman 1978). In making these estimates, the Agency had to choose between two basic approaches. One possible way was to assume that the U.S. population would be exposed to the highest residues of amitraz that would be legally permissable (i.e., at the tolerance), and to calculate the maximum residue exposure for each individual. The other approach was to assume that the national population might be exposed to the average of residue levels actually measured in field tests. Since there are ample data for determining the actual residue levels of amitraz, the Agency believed that the latter approach was more reasonable and representative of the exposures that may be anticipated by the public. However, maximum exposures based on the tolerance were also calculated for purposes of comparison.

Having chosen the average residues as the data base, other assumptions were made: first, residues in processed fruit would be one-fourth of the level in fresh fruit*/; second, every exposed person eats a standard diet which includes about 109 apples and 11 pears per year; and third, the average person weighs about 60 kilograms.

Using these assumptions, the estimated daily ingested doses of amitraz were in Table 2 as follows. First, the residue of amitraz in a fruit, measured in parts of amitraz per million parts of the fruit (column 1) was multiplied by the grams of fruit that the average person eats per day (column 2). The consumption levels were derived from an extensive Food and Drug Administration survey in 1965-1966 (Schmitt 1978). For apples, the food factor was 50.13

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*/ The Boots-Upjohn rebuttal submitted data confirming that about 75% of the amitraz residues in a pear are contained in the peel. Therefore, if the peel is removed during processing, only about 25% of the amitraz residues should remain in the pulp. In the absence of similar data, it is assumed that the same phenomenon occurs in apples.

g/person/day and for pears it was 5.06 g/person/day. If an average pear or apple weighs about 168 g (6 oz.) then these figures translate into about 109 apples and 11 pears per person per year (including fresh, processed and juice products). Next, the product of the first step was multiplied by the percent of the total bearing crop assumed to be treated with amitraz (column 3). The product of this step was then divided by 60 kg, the average weight of a person, to obtain the daily intake of amitraz (column 4).

Table 2 assumes equal distribution of fruit across the U.S. and an average consumption of fruit by individuals. Although some people may consume more treated pears due to their eating habits or geographical location, the risks for these persons would probably not be significantly higher than for the average person. For instance, if a person lived in an area where all pears sold had been treated, that person's exposure would be about two times the average, since only about half of the U.S. pear acres are predicted to be treated. (Also, because the risks for amitraz are directly proportional to exposure, this person's risk would be doubled.) Another example would be a person eating twice as many pears as the average; his/her risk would also be twice the average. In any event, while some individuals could have exposures higher than the average, these exposures and the associated risks would not be excessively greater than the average. Further, as discussed in Part III.D. (Food Exposure), the total number of potential cancer cases remain the same for the total U.S. population, regardless of variation in individual exposures.

Another large data base concerning amitraz residues in pears was collected and analyzed in 1977-1978 in a cooperative study by Oregon, Washington, and California research personnel, the National Monitoring and Residue Analysis Laboratory (NMRAL) of the Animal and Plant Health Inspection Service of the USDA, and the Upjohn Company. Pears were treated with amitraz at four research stations and harvested 7 or more days after the last application. The pears were either immediately frozen, or washed and waxed, or stored for various periods or canned. A total of 98 samples were shipped to the NMRAL, where part of every sample was removed and forwarded to the Upjohn Company for duplicate analysis. Appendix 2 summarizes the results. Because this survey sampled pears at least 7 or more days after the last treatment with amitraz, and because the Upjohn Company had applied for registration at a 1-day treatment-to-harvest interval, the Agency did not estimate ingestion exposure based on these data. However, in section IV.C.2. of this document, the study results were used to demonstrate the potential residue reduction achievable by lengthening the preharvest interval.

Table 2. Dietary Exposure to Amitraz

Product	1/ Residues (ppm)	2/ Average Consumption (g/person/day)	3/ Portion of Crop Treated (percent)	Estimated Daily Intake of Amitraz (ug/kg/day)
Apples		50.13	10 (total)	
Fresh	3.0 (max.)		5.5	0.14
	0.71 (avg.)		"	0.03
Processed	0.75 (max.)		4.5	0.03
	0.19 (avg.)		"	0.007
Pears		5.06	68 (total)	
Fresh	3.0 (max.)		35	0.09
	1.0 (avg.)		"	0.03
Processed	0.75 (max.)		33	0.02
	0.25 (avg.)		"	0.007

1/ Based on actual residue values reported by Upjohn Company, 1977.
2/ Schmitt, 1978. These figures were derived from a Food and Drug Adminstration household survey of 1965-1966.
3/ Luttner, 1978.

2. Occupational Exposure

Table 3 summarizes exposure estimates for pesticide applicators, farm workers and persons downwind from treated areas.

Column 1 identifies the exposed groups. They include about 1,400 apple growers, 3,200 pear growers, an unknown number of commercial helicopter applicators and an unknown number of farm workers or persons downwind from applications.

Column 2 divides the routes of exposure into dermal (skin) and respiratory (upper respiratory passages and lungs.

Exposure rates (e.g., milligrams of amitraz per unit of time or quantity) that may occur are listed in column 3. Here, the rates for two exposed groups were based on data for amitraz itself. The dermal exposure to applicators during mixing and loading was calculated as 9 milligrams per drop based on the weight of 1.5 pounds of amitraz per gallon of undiluted BAAM (Mittelman 1978). Dermal exposure to farm workers (e.g., pickers, pruners, etc.) was assumed to be negligible, since amitraz residues on treated leaves were not detected in a field study (Wolfe 1978).

Due to lack of definitive data, all other exposure rates in column 3 had to be derived from data for pesticides other than amitraz. The inhalation of 0.04 mg/hr for mixers and loaders was calculated by using data for parathion -- 0.02 mg/m^3 parathion measured in air during mixing and loading (Batchelor and Walker 1953) -- and assuming a moderate respiratory rate of 1.8 m^3/hr. To estimate dermal exposures for groundspray applicators, residue values measured from dermal pads worn during air-blast applications of 12 pesticides (Wolfe et al. 1967, 1972) were averaged; these were assumed to give a rough indication of what skin exposure can be expected from amitraz (Garner 1978). It was also assumed that a ground spray applicator would have his face, back of neck, "V" of chest, forearms and hands exposed (2940 cm^2). For exposure to pilots during aerial application, data for endrin during fixed-wing aircraft applications (Jegier 1964) were used. Those data showed that pilots were contacting endrin dermally at 1.8 mg/hr and by inhalation at 0.08 mg/hr. Assuming similarity of droplet size distribution and adjusting for the maximum application rate of amitraz gave the figures in the table. Helicopters would likely be the preferred method of aerial application, due to their greater penetration of the orchard canopy. Since there were no data available for helicopters, the Agency had to assume that the fixed-wing aircraft data would give a rough indication of exposure from helicopter operations.

Column 4 of Table 2 estimates the average duration of each occupational situation. The exposure periods for groundspray applicators were calculated by the equation:

$$\frac{\text{Acres treated}}{\text{Number of growers}} \times \frac{\text{Number of applications per year}}{\text{Treatment Rate (acres/hr)}} = \text{Hrs/Grower/Yr}$$

This assumes that each grower treats one average-sized orchard per year. For example, for apples:

$$\frac{52{,}000 \text{ acres}}{1{,}400 \text{ growers}} \times \frac{1 \text{ application/yr}}{4 \text{ acres/hr}} = 9 \text{ hrs/grower/yr}$$

Because of a lack of data, the exposure times for all exposure situations other than groundspray applicators were not calculated by this equation; instead, they had to be assumed.

Column 5 lists the estimated maximum amounts of amitraz that may be absorbed into the body by the various routes of exposure. To make these estimates the Agency reviewed toxicological data on amitraz to determine the potential penetrability of amitraz through the skin and through respiration into the bloodstream (Budd 1978). From this review, the Agency has adopted the following worst-case assumptions: first, up to 50% of an amitraz dose may be absorbed through unprotected skin; second, 50% of the amount of amitraz inhaled may be deposited in the upper respiratory passages and swallowed; third, 100% of amitraz that is swallowed after inhalation is absorbed through the gastrointestinal tract; and fourth, 25% of the amount inhaled may reach the lower parts of the lungs and be absorbed there. Using these assumptions and 60 kg as the average weight of a person, the Agency calculated the figures in column 5. Footnote 2 of the table gives the equation for this calculation.

Growers using groundspray equipment have the highest potential exposure to amitraz through dermal contact with either the concentrated formulation during mixing and loading, or from the the spray mist. One drop of undiluted BAAM on the skin could result in a dose of 0.075 mg/kg. A larger spill of 10 ml would give a dose of 3.8 mg/kg. A pear grower making two applications in a year would absorb 1.53 mg/kg of the active ingredient amitraz during the applications; an apple grower applying amitraz once a year would absorb 1.26 mg/kg of amitraz (Garner 1978). In contrast, the amounts of amitraz swallowed after inhalation or the quantities absorbed through the lungs would be far less. During application, it was estimated that for both pear and apple groundspray applicators, about 0.002 mg/kg/yr amitraz would be swallowed and 0.001 mg/kg/yr would penetrate through the lungs.

In 1977, EPA monitored BAAM applicators and measured dermal and inhalation exposures (Davis 1978). However, the authors of that study felt that the results may not have been representative of normal applicator practices. They stated that the applicators who were wearing a full set of protective rain gear did not avoid drifting spray. Therefore, they were probably more careless in general than applicators who wore less equipment. This led to a great range in the dermal exposure for the fully protected applicators (0.175 mg/hr to 250 mg/hr; mean = 31.8 mg/hr). Also, several applicators inadvertantly contaminated detection pads in their respirators, further exaggerating the respiratory exposure (0.075 mg/hr to 865 mg/hr; mean = 75.5 mg/hr). Because of these anomalous results, the Agency did not use these data to estimate exposures ~~to~~ groundspray applicators.

Commercial applicators using helicopters are estimated to receive very low doses of amitraz: 0.05 to 0.07 mg/kg/day from dermal contact, 0.0035 to 0.0045 mg/kg/day from swallowing after inhalation and 0.00175 to 0.00225 mg/kg/day from lung penetration by spray mist (Garner, 1978a). Treatments for apples and pears take 7 and 3 minutes, respectively, given that a helicopter may cover 5.25 acres per minute and given average orchard sizes (Garner 1978c). The total number of applicators who might apply by helicopter and the number of groves they might treat are unknown. However, helicopter applications would probably be infrequent. (Garner 1978c).

The Agency's monitoring of 1977 spraying operations revealed no dislodgable or nondislodgable residues on the tree leaves after they had dried (Davis 1978). Therefore, the Agency assumes that no exposure would occur for workers reentering a treated area after the leaves are dry.

Once sprayed into the air, amitraz will drift according to the wind pattern and may be deposited away from the site of application. Assuming a usual distribution of a spray of medium-size droplets applied by multiple passes over an area, and using data for the pesticide endrin, the potential dermal dose of amitraz would be 0.0025 to 0.0034 mg/kg for a normally-clothed person standing 1/4 mile downwind for an entire treatment of an average-sized farm (Garner 1978a).

3. Conclusions on Exposure Data

The reliability and meaning of the dietary and occupational exposure estimates vary according to the data and assumptions upon which they were based. Since dietary exposures were derived from actual average residues in fresh and processed fruit, on standard food factors and on the estimates of acres treated with amitraz, they should be considered fairly accurate. Occupational exposures, on the other hand, were mostly derived from data for other pesticides and based upon worst-case assumptions about the penetrability of amitraz into the body.

If it is assumed that the dietary and occupational exposure estimates are reasonable, then it appears that the highest doses which may be received are through the skin during mixing and loading and during application. Much lower doses result from respiration of amitraz during these same activities. Similarly, the doses resulting from ingestion of amitraz residues after eating treated fruit are very small. No exposure is expected for farm workers (as long as a reentry period is observed) and very little exposure is anticipated for persons not in the immediate application area. Column 5 of Table 4 compares lifetime doses.

D. Quantitative Risk Estimates

The Interim Cancer Guidelines state that when a chemical is judged to be a potential human carcinogen, the Agency will make estimates of its possible impact on public health at anticipated levels of exposure. These guidelines also recognize that the available techniques for assessing the magnitutde of cancer risk to human populations based on animal data are at best very crude;

Table 3. Occupational Exposure to Amitraz

Population	Route	Estimated Rate of Exposure 1/	Exposure Duration	Maximum Amount of Amitraz Absorbed 2/
Mixers and Loaders				
1,400 apple growers and 3,200 pear growers 3/	dermal respiratory	9.0 mg/drop 0.04 mg/hr	------- Assume 1 hr	4.5 mg/drop 0.00033 mg/kg/hr (swallowed) 0.00016 mg/kg/hr (lungs)
Groundspray Applicators				
1,400 apple growers	dermal respiratory	19 mg/hr 0.03 mg/hr	9 hrs/day X 1 day/yr 3/	1.26 mg/kg/yr 0.002 " (swallowed) 0.001 " (lungs)
1,500 pear growers	dermal respiratory	23 mg/hr 0.03 mg/hr	4 hrs/day X 1 day/yr 3/	0.77 mg/kg/yr 0.001 " (swallowed) 0.0005 " (lungs)
1,700 pear growers	dermal respiratory	23 mg/hr 0.04 mg/hr	4 hrs/day X 1 day/yr 3/	1.53 mg/kg/yr 0.002 " (swallowed) 0.001 " (lungs)
Helicopter Applicators				
Apples	dermal respiratory	0.66 mg/hr 0.03 mg/hr	Assume 1 day/yr	0.05 mg/kg/yr. 0.0035 " (swallowed) 0.00175 " (lungs)
Pears	dermal respiratory	0.66 mg/hr 0.03 mg/hr	Assume 1 day/yr	0.07 " 0.0045 " (swallowed) 0.00225 " (lungs)
Pickers	dermal	0 4/	Assume leaves are dried	0 "
Persons 1/4 mile Downwind from Spray				
Apples	dermal	0.0025 mg/kg	Assume 1 day	
Pears	"	0.0034		

1/ Unless otherwise noted, the source of these data are Mittelman, 1978.

2/ Amounts absorbed are calculated as follows: [Exposure (mg) X Duration of Exposure (hrs/yr) X Percent of Absorption by the Route of Exposure]/Average Bodyweight (60 kg). Dermal absorption is estimate to be 50% at most (Budd 1978). When a dose of amitraz is inhaled, as much as 50% of it may be swallowed and 25% may penetrate the lungs (Budd 1978).

3/ Luttner, 1978.

4/ Davis, [illegible]

this is due, among other causes, to uncertainties in the extrapolation of dose-response data to very low dose levels and due to differences in levels of susceptibility of animals and humans. Accordingly, the risk estimates are neither scientific certainties nor absolute upper limits, but are used by the Agency only as rough approximations of potential health risks.

The CAG's risk estimates are in Table 4. They are based on the following data and assumptions:

Bioassay Data Used -- The CAG chose to base its risk estimates on the LR tumor incidences in female mice reported by the various pathologists, because all the diagnoses were statistically significant (Albert 1978e). The CAG determined that the diagnoses by Dr. Reuber of LR tumors and malignant liver tumors in male mice were not appropriate for quantitatively estimating risk, due to the reasons stated in Part III.C. Lack of information about the quantities of 2,4-dimethylaniline that may be formed during ingestion of amitraz precluded the CAG from estimating any risks for that compound.

The histopathological reviews of the Boots Study slides by Drs. Dubin and Squire together (for EPA), Dr. Reuber (for EPA) and Boots-Upjohn resulted in a range of incidences of diagnosed LR tumors in the high dose and control female mice (Albert 1978d). The risks in Table 3 are based on Dr. Reuber's LR tumor counts, which are the highest of the three diagnoses. Using the diagnoses of the other pathologists would result in lower risks: 40% less risk using Boots-Upjohn's numbers and 56% less risk using the Dubin-Squire diagnosis.

Reliability of the Boots Mouse Study -- The CAG has concluded that the Boots Mouse Study is less than ideal due to the uncertainties associated with its protocols noted above. However, if it is assumed that the LR tumor counts of the Boots Mouse Study are definitive, then hypothetical risks can be estimated.

Risk Extrapolation Model -- The one-hit model (also called the linear non-threshold model) was used to calculate the mathematical probability that an individual will develop a tumor due to exposure to amitraz

Table 4. Potential Cancer Risks Through Dietary and Occupational Exposure to Amitraz 1/

Population At Risk	Number Exposed	Route of Exposure	Average Lifetime Dose 2/	Individual's Lifetime Chance of Cancer 3/	Maximum Potential Cancer Cases per Year 3/
U.S. population	2.2×10^8	Ingestion:			
		Apples	0.001414 ppm	2×10^{-6}	8
		Pears	0.001102 "	2×10^{-6}	6
Groundspray Applicators					
Apples	1,400	dermal	0.0689 ppm	1×10^{-4}	0.002
Pears:					
(1 application)	1,500	dermal	0.0370 "	6×10^{-5}	0.001
(2 applications)	1,700	dermal	0.0740 "	1×10^{-4}	0.003
Helicopter Applicators					
Apples	---	dermal, inhalation and swallowing	0.0027 ppm 4/	2.79×10^{-6}	<0.0001
Pears	---	dermal inhalation and swallowing	0.0037 "	3.88×10^{-6}	<0.0001

1/ Albert 1978e.

2/ Figures in this column are lifetime average exposures expressed as equivalent ppm in the diet for a lifetime (70 years), in the case of the U.S. population, and for a 40 year working history for applicators.

3/ These risk estimates are based on Dr. Reuber's diagnoses of lymphosarcoma incidences, which were the highest among several pathologists.

4/ While an average pear or apple orchard requires only a few minutes to treat, it is reasonable to assume that a commercial applicator might spend 1 day per year treating several orchards.

in that person's lifetime. From the individual risk estimates the CAG calculated the number of cancer cases expected for an exposed population.

$$\text{Risk} = 1 - e^{Bx}$$
$$B = (1/y)\ln[1/(1-P)]$$

Where: B = slope coefficient of the one-hit model
$P = (Pt-Pc)/(1-Pc)$
Pc = incidence of LR tumors in control animals
Pt = incidence of LR tumors in test animals
y = test animal exposure (ppm)
x = potential human exposure (ppm)

Food Exposure -- Ingestion exposures are based on the averages of actual residue data obtained during 1974-1976 and on the assumption than an average person will consume 109 apples and 11 pears per year. These exposure estimates also assume an average distribution of fruit among the U.S. population. Consequently, if one were to eat more or fewer apples and pears than the average person, or if one were to eat fruit with more or less than the average residue, then one's risk would increase or decrease in direct proportion to the amount consumed annually. For example, a person eating 22 pears a year would incur twice the risk listed in Table 4. Similarly, a person eating fresh apples with 0.35 ppm (half of the average) amitraz residues would incur half the risk listed in Table 4. It should be pointed out that the total number of potential cancer cases would remain the same regardless of the variations in individual eating habits, since the total amount of amitraz applied in a year may only cause a certain number of cases.

Occupational Exposure -- Applicator exposure figures are estimated from other pesticide data for skin or respiration exposure. Zero exposure for field workers is based on field data for amitraz and on the assumption that they would not enter a treated area until the leaves are dry [Such a requirement is contemplated later in this document].

It is apparent from the hypothetical risk estimates that the lifetime cancer risks for individuals consuming treated fruit are quite small (10^{-6}), with the risks being one to two orders of magnitude higher for applicators (10^{-4} to 10^{-5}). However, the total number of cancer cases per year is much higher for the U.S. population consuming treated apples and pears than for applicators (14 cases/yr vs. 0.006 cases/yr). This is due to the great disparity of size between the U.S. population (220,000,000) and the applicator population (5,000).

E. Risks from Substitute Pesticides

The Agency has evaluated the risks of registered substitute pesticides in order to determine their risks relative to amitraz. These compounds are identified in Part III. B.2 of this document.

Two EPA documents concern the risks of the major substitutes. "Toxicology Data on Alternative Pesticides to BAAM" provided a summary of the published and proprietary animal toxicity data relevant to potential human hazards of the major substitutes (Dale 1978a; Dale 1978b). "Revised Fish and Wildlife Risk Analysis for BAAM" (Bushong 1978) evaluated the potential effects of the major substitutes on terrestrial and aquatic organisms. Table 5 summarizes the potential hazards of humans and the environment, as well as data gaps for each of the major substitutes.

III. Benefit Analysis

The applicant for registration has proposed that amitraz be registered for control of certain pests on apples and pears. In this section, the Agency examines the potential usage of amitraz on these crops if it were to be registered, the availability and comparative efficacy and costs of alternative pest control programs, and the projected impacts on growers and consumers of pear and apples if amitraz were not available.

While substantial empirical data were available for purposes of making an assessment of the economic impact of denying the use of amitraz on apples, limited empirical data were available for purposes of making a similar assessment for pears. Therefore, assumptions were made about the efficacy of amitraz compared to substitute pesticides used on pears, and gross estimates were made of the economic impacts that might result if amitraz were not available for use on pears.

The Agency depended upon a team of agricultural specialists from the U.S. Department of Agriculture and the EPA to collect test plot data, to evaluate that data and to

Table 5. Potential Human and Environmental Hazards from the Major Substitutes Pesticides for Amitraz

Chemical	Crop	Hazards to Humans 1/	Environmental Hazards 2/	Data Gaps 1,2/
propargite	apples	No known hazards of concern	10-100 times more toxic to fish and estuarine species than amitraz. Accumulates 80-100 times more than amitraz. Exposure to these species is unknown.	Oncogenesis Mutagenesis Neurotoxicity Aquatic invertebrates
cyhexatin	apples	No known hazards of concern	Some hazard to birds and aquatic invertebrates. 1,000-fold more toxic to fish than amitraz. Exposure to these species is unknown.	Acute dermal Acute inhalation Skin irritation Estaurine species Accumulation study
mineral oil 3/	pears	No known hazards of concern	Probably less hazardous than amitraz for all species and the least hazardous of substitutes for amitraz.	Acute, subacute, chronic studies. Mutagenesis.
chlordimeform 4/	pears	Parent compound and two metabolites are oncogenic.	Not known.	Not known.
endosulfan 3/	pears	Acute and chronic studies show female animals are more sensitive to the pesticide than male. Chronic studies show possible kidney and liver effects at 100 ppm but not at 30 ppm. However, there is no basis for an RPAR.	More toxic to all fish and wildlife than amitraz. It accumulates to higher levels than amitraz, but dissipates quickly and therefore does not present a food web hazard. Exposure to fish and wildlife is unknown.	Oncogenesis (Long-term feeding) Mutagenesis Teratogenesis
mancozeb 3/ and zineb	pears	These chemicals have been RPAR'ed for oncogenicity, teratogenicity and mutagenicity	Mancozeb may be more hazardous than amitraz due to higher application rates. Data are not available for comparing zineb to amitraz. Exposure to fish and wildlife is unknown.	Aquatic species (for mancozeb) Accumulation and field studies for zineb

make economic estimates based either on that data or their best judgment. Basically, there were two impact assessments. One was performed by EPA in March, 1977, to indicate the impacts of approving or disapproving applications for the emergency use of amitraz on pears in Oregon and Washington for the summer of 1977 (Luttner 1977). The other analysis was conducted by USDA and EPA from May, 1977 to August, 1978 to evaluate the impacts of the unavailability of amitraz for pears and apples (USDA/State Assessment Team 1978).

Sections A and B discuss the results of these analyses. Section C presents the Agency's judgment on the quality of the data and on the relative weight which the Agency places on the economic estimates of the benefits of amitraz.

A. Apples

All data and estimates discussed on apples are from the USDA/State Assessment Team Report on Amitraz, 1978.

1. Estimated Usage

Under the proposed label, amitraz would be used on apples primarily to control European red mites, apple rust mites and two-spotted spider mites. The material would also suppress certain other pests including codling moths, white apple leafhoppers, tentiform leafminers, apple maggots, apple aphids and McDaniel mites.

Amitraz, formulated as BAAM EC (containing 1.5 lbs. a.i. per gallon), would be applied to apples at these rates:

1. 2 to 2.5 quarts per acre (dilute coverage) or 1 to 1.25 pints per 100 gallons water (concentrate spray) to control European red and apple rust mites.
2. 2.5 to 3 quarts per acre (dilute coverage) or 1.25 to 1.5 pints per 100 gallons water (concentrate spray) to control two-spotted mites.

Due to its broad-spectrum acaricidal activity, amitraz kills beneficial (predator) mites as well as the target mite species. In Washington, Oregon and California, pest mite populations in apples are kept under control mostly by an integrated pest management (IPM) program in which predator mites play a significant role. Predator mite populations are maintained at efficacious levels by minimum use of broad-spectrum insecticides and judicious use of registered acaricides. Due to the success of this mite IPM program, amitraz is not expected to be used in these states.

However, in the apple-producing areas of the Eastern and North-Central states, integrated pest management programs for mite control are not as well established.*/ As a result, several registered acaricides are routinely used in many areas for mite control. Broad-spectrum organophosphate insecticides, routinely used to control such pests as aphids, apple maggots and scales, further reduce the predator mite populations. State research and Extension Service personnel have indicated a need for an additional material to rotate with other popular apple miticides to minimize potential mite resistance. Based on this information, amitraz might be adopted for use by some growers in the Eastern and North-Central states. However, further advances in integrated pest management in the Eastern states may eventually limit the use of broad-spectrum acaricides and insecticides.

Since another miticide might be used by growers in the East and North-Central states, it was assumed that amitraz would enter the market previously held by chlordimeform; this compound was removed from the market by its manufacturers in 1976. Public and confidential Doane Crop Specialty Surveys of 1972-1974 showed that, had chlordimeform remained available through 1978, it may have been used on as much as 10% of the domestic apple acreage. This figure approximates the market penetration estimate of 10.3% for amitraz submitted by the Upjohn Co. in its rebuttal; therefore, it was assumed that they represented the maximum amitraz use level on apples if amitraz were available to growers in 1978.

Assuming that amitraz may be used on up to 10% of U.S. apple acreage, a maximum of 52,000 acres of the total 521,000 domestic acres would be treated with the material in the near term. Since amitraz would only be used in the Eastern and North-Central states, these 52,000 acres are actually 15.1% of the 344,000 acres in those states. At the proposed label rate of 2 to 2 1/2 quarts BAAM EC per acre, up to 44,000 lbs. of amitraz active ingredient would be required to treat the 52,000 acres of apples.

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*/ These areas include the following states: CT, DE, IL, IN, MA, MD, ME, NH, NJ, NY, NC, OR, PA, RI, SC, VT, VA, WV, WI.

2. Alternative Methods of Pest Control

State recommendations and Federal guidelines suggest several miticides for use on apples. Cyhexatin (Plictran) and propargite (Omite) are the most widely used materials. Cyhexatin is the single most widely used miticide on apples; in 1975, 300,000 lbs. of propargite were applied to 200,000 acres of domestic apples, 38% of the total acres grown. Table 6 lists these and other registered but less used pesticides on apples.

According to State research and USDA Extension Service personnel, a variety of integrated pest management (IPM) methods and currently available materials satisfactorily control apple mites. IPM methods have proven effective and are well established in three Western states, Washington, Oregon and California. In these states, apple rust mites are permitted to develop in the early part of the growing season, since apples can withstand without damage relatively high apple rust mite populations. These rust mites act as a food source for predator mites which, as the season progresses, multiply to population levels capable of controlling the major pest mites of the summer period (two-spotted mites, McDaniel mites and European red mites). Acaricides and organophosphate pesticides which damage predator mites are used only minimally.

Integrated pest management methods have also been effective in many areas of the Eastern apple growing region, e.g., Michigan and Pennsylvania. Further advances in IPM control strategies in the Eastern states may eventually limit the need for the broad-spectrum acaricides and insecticides now in use.

There are at least nine field trials which have compared the efficacy of amitraz with currently used apple miticides such as cyhexatin and propargite. The test results were presented in terms of pest mite populations remaining per leaf after specified treatment dates. Although the test results varied, a majority of the studies indicated that the alternative materials provide a level of mite control at least comparable to that of amitraz. Both cyhexatin and propargite dominate the present apple miticide market and cost less to use per acre than amitraz. Table 7 shows their comparative costs.

Table 6. EPA Registered Contruls for European Red Mite Apple Rust Mite and Two-Spotted Spider Mite on Apples

Pesticides	European Red Mite	Apple Rust Mite	Two-Spotted Spider Mite
azinphosmethyl[2]	X	X	X
carbaryl[2]	X	X	X
carbophenothion[2]	X	-	X
chlordimeform	X	X	X
chloropropylate	X	-	X
cyhexatin	X	X	X
demeton	X	X	X
diazinon	X	-	X
dicofol	X	X	X
dimethoate	X	-	X
dormant oil	X	X	X
endosulfan[2]	X	X	X
fenbutatin-oxide	X	X	X
fortenate hydrochloride	X	-	X
lime sulfur	-	X	X
malathion[2]	X	X	X
oil (superior type)	X	X	X
phosalone	X	-	X
phosmet[3]	X	-	X
propargite	X	-	X
sulfur	X	X	-
tetradifon[2]	X	X	X

2/ Includes mixture registrations.
3/ Suppression only.

Table 7: Comparative Costs of Amitraz, Cyhexatin and Propargite

Miticide	Cost 1/	Rate/Acre 2/	Cost/Acre 3/
amitraz 1.5 EC	$38.50/gal	2.25 qts	$21.66
cyhexatin 50 WP	$12.00/lb	1.25 lbs.	$15.00
propargite 30 WP	$2.25/bl	5 lbs.	$11.25

1/ The amitraz price represents average 1977 growers level cost in Western states, which is similar to the expected cost for Eastern growers in 1978.

2/ Per acre application rates are averages taken from various state apple pest control guides.

3/ Product of [miticide cost per unit] X [rate per acre]. Cost data include pesticide materials only; application method and cost were assumed to be the same for amitraz and alternative miticides.

About 22,000 pounds of cyhexatin and 25,500 pounds of propargite would be used on the 52,000 affected acres if amitraz were not available.

3. Impacts

a. Growers

The unavailability of amitraz will have no apparent economic effects on apple growers. A variety of registered materials which are of equal or greater efficacy against apple mites are available. All of these materials are less expensive than amitraz. If amitraz were used on 52,000 acres of domestic apples, the total cost to the industry would be $1,126,320 (52,000 A X $21.66). Assuming that 2/3 of the 52,000 acres were treated with cyhexatin and 1/3 with propargite, the per acre costs would be:

cyhexatin = 35,000 X $15.00/acre = $525,000
propargite = 17,000 X $11.25/acre = $191,250
Total cost of substitutes $716,250

Thus, using amitraz would increase control costs by $410,070 or an average per acre increase of $7.89. Since the average farm size for Eastern and North Central apple orchards is 36.4 acres, the grower adopting amitraz for use on 100% of the orchard would pay about $287 more per year.

Because the availability of amitraz would have essentially no effect on the quality or quantity of apples, the treatment cost increases would not be offset by revenue gains, and would thus reduce grower's net returns.

The only potential negative impact from the lack of amitraz would be the unavailability of an additional material to rotate with current miticides to minimize the problem of mite resistance. The extent of this problem is not known, but is believed to be of minor significance.

b. Consumers

The unavailability of amitraz for use on apples will have no effect on the consumer. Because available substitutes are as efficacious as amitraz to control apple mites, no reduction in quantity or quality of fruit is expected. Since the substitutes are less expensive than amitraz, no retail effects are anticipated.

B. Pears

As indicated earlier, there were two economic analyses performed to assess the potential impacts of the unavailability of amitraz for summer control of pear psylla.

The first was conducted by EPA early in 1977 to determine the potential economic impacts of the unavailability of amitraz for the summer of 1977 in Oregon and Washington (Luttner 1977). The assessment was performed to provide data for a determination on requests from these states for an emergency exemption. The circumstances required rapid action, and so the assessment was limited in scope and detail. On the basis of professional opinions of USDA and State research and extension personnel, the EPA concluded that the registered alternative pesticides were ineffective. Actual test plot data was also interpreted to indicate that amitraz was as efficacious as chlordimeform (Galecron, Fundal), which had been voluntarily withdrawn from the market in 1976. Using the damage levels, acreages, treatment schedules and cost data estimated by the USDA agricultural specialists in the affected states, the EPA calculated the impacts on growers of increased pesticide costs and pear crop value reductions to be about $5,000,000 in Oregon and $8,200,000 in Washington in 1977. Other general conclusions were that the sharp decline in production would lead to increased wholesale and retail prices of fresh pears. Also, increased quantities of process grade pears might lead to depressed grower, wholesale and retail prices for canned and other processed pears.

The 1978 USDA/State Assessment Team Report is the second and more extensive economic evaluation of amitraz on pear psylla. This analysis consisted of two basic steps. The first step estimated the economic impacts of the unavailability of amitraz for 1977; the second step projected losses that might occur in 1978-1981.

To create a data base for the 1977 estimates, the USDA and State Research and Extension Service personnel established test plots in 1977 in the pear-growing areas of Wenatchee, Washington, Hood River and Medford, Oregon, and Mendocino County (Hopeland), California. From these plots, data on the cost of application, efficacy against pear psylla, and pear yield and quality were collected; these data were compared with alternative spray programs. While the protocols varied by location, they generally included: unreplicated 1/2 acre blocks of amitraz and the alternative standard spray programs; visual examination of fruit for psylla russet; measurement of quality by firmness and soluble solids in juice; counts of adult psylla, eggs and nymphs on the trees; and a calculation of the costs of applications.

These plot data were the basis for the 1977 economic input estimates. The 1978-1981 economic impact projections did not rely directly upon the plot data, but were developed from estimates by USDA and State agricultural experts. Other essential assumptions, procedures and results of the 1977 and 1978-81 impact analyses were:

-- Amitraz is a new material; therefore, the number of acres to which amitraz might be applied had to be assumed. For this analysis, the assumption was made that all bearing acres in Oregon and Washington, and 35% of the bearing acres in California, would be treated annually. This assumption was based on the apparent lack of an efficacious alternative insecticide for summer control of pear psylla.

-- The 1974-1976 average acreage, production, and value of pears were estimated and assumed to represent the acres, production, and value of pears in the 1977-81 analysis period.

-- Partial budgets, developed by research and USDA Extension service personnel in respective areas and based upon the test plot data, were used to estimate cost differences of amitraz and alternative insect-control programs.

--Estimates were made of 1978 losses due to pear quality damage and decreased production. Assumptions were then made about the percent yearly increases in losses through 1981.

1. Estimated Usage

Under the proposed label amitraz would be applied to pears for the control of summer pear psylla at these rates:

1. air carrier dilute sprays -- 1.1 to 1.5 lbs. active ingredient of amitraz (3 quarts to 1 gallon of 19.8% amitraz formulated as an emulsifiable concentrate) in 200 to 400 gallons water/acre.
2. air carrier semi-concentrate sprays -- 1.1 to 1.5 lbs. amitraz in 50 gallons water/acre.

The control of summer pear psylla is a major pest problem in three western states: California, Washington, and Oregon. In these three states, 91,000 acres of pear orchards are cultivated, 67,600 acres in Bartletts and 23,400 acres in various winter varieties. Amitraz could be used for the control of summer pear psylla in these three states because currently registered insecticides may not provide economic levels of control. At this time, there are no other new pesticides under consideration for registration to control pear psylla.

An estimated 54,700 acres of pears would be treated annually with amitraz; this is based on the assumption that 35 percent of bearing acres in California and all of the bearing acres in Oregon and Washington would be sprayed for pear psylla. The amounts of amitraz to be applied per acre as well as the acres treated were based on the professional judgments of State research and Extension Service personnel:

Amitraz use in Oregon on 20,076 acres:

20,076A X 2 applications of 1.5 lbs. amitraz/A = 60,228 lbs. amitraz.

Amitraz use in Washington on 21,736 acres:

21,736 A X 24% X 2 applications of 1.5 lbs. amitraz/A = 15,651 lbs. amitraz.

21,736 X 76% X 1 application of 1.5 lbs amitraz/A = 24,779 lbs. amitraz.

15,651 lbs. + 24,779 lbs. = 40,430 lbs. amitraz.

Amitraz use in California on 12,840 acres:

12,840 A X 25% X 2 applications of
1.125 lbs. amitraz/A = 7,223 lbs. amitraz.

12,840 X 75% X 1 application of 1.125 lbs. amitraz/A =
10,834 lbs. amitraz.

7,223 lbs. + 10,834 lbs. = 18,057 lbs. amitraz.

Total use of amitraz on 54,652 acres:

Oregon = 60,228 lbs.
Washington = 40,430 lbs.
California = 18,057 lbs.
118,715 lbs.

2. Alternative Methods of Pest Control

Prior to its withdrawal from the market, chlordimeform was apparently the most commonly used material for summer control of pear psylla. There is little information on the efficacy of the registered alternatives. Amitraz is thought to be the only effective material now under consideration for registration to replace chlordimeform.*/ A variety of IPM methods have been tested and apparently proven ineffective for the summer control of pear psylla in many areas of Washington, Oregon and California. During the absence of chlordimeform in 1977, several registered insecticides (endosulfan, perthane, phosmet, mancozeb, zolone, azinphosmethyl, oils, morestan, pyrenone, toxaphene, parathion and zineb) were applied to pear orchards and apparently were only partially effective.—/

3. Impacts

a. Growers

Estimates of the impact of the unavailability of amitraz in 1977 were based on the test plots already described. The specific kinds of data collected from the four locations varied, but basically included some measure of pest infestation and pear quality or damage. Only

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*/ On November 8, 1978, the Agency approved the emergency use of an unregistered material, pydrin, on pear psylla in eight pear-producing states. However, pydrin may not be used during the summer, which is when amitraz would be mostly applied, since data have not shown it to be efficacious. Further, no registrant has applied for registration of pydrin for pear psylla.

Hopeland, CA did not report quantitative data on damage. USDA research and extension specialists interpreted these data. For Bartlett and d'Anjou pears in Wenatchee, there were fewer pear psylla and less pear damage in the amitraz-treated plots than in the standard spray plots using Dithane M45 (mancozeb) and Thiodan (endosulfan). On Bosc and Comice pears in Medford, Oregon, the post-treatment density of immature psylla were lower in the amitraz-treated pears than in the pears of the standard spray program (endosulfan and zineb). Almost half of the Comice pears in the standard group were downgraded from U.S. #1 to Fancy or culls, whereas only 5% of the amitraz-treated Comice pears were downgraded. Bosc pears from the standard program were downgraded 11% compared to 1% of the amitraz program pears.

In contrast, the test plots in Hopeland, California and Hood River, Oregon, showed no differences in quality losses due to pear psylla between the amitraz and alternative spray programs in 1977. Agricultural specialists in those areas felt the test plot results were atypical. They attributed the lack of a difference between amitraz and alternative treatments to low pear psylla populations in the test plots, and late availability of amitraz; this resulted in an abbreviated spray schedule. Therefore differences between the amitraz and alternative control programs in other producing areas may be smaller than would have occurred had amitraz been available at the beginning of the normal spray season. For these reasons, the specialists believed that use of the test plot data from Hopeland and Hood River would have underestimated the 1977 losses.

Before estimating the potential impacts of the unavailability of amitraz, USDA economists had to develop partial budgets to estimate the cost differences between amitraz and alternative control programs in each pear growing area.

From these interpretations of the test plot data and using the partial budgets, the Assessment Team estimated that, had amitraz not been available, returns to pear producers would have been reduced $3,728,300 in 1977 (Table 8). Of this amount, 60% of the loss would have been due to pears being downgraded from U.S. Grade #1 to U.S. Grade #2; 40% of the loss would have been due to increase in cull or unmarketable pears.

Estimates of losses that might be incurred during 1978-81 if amitraz were unavailable were also made by USDA/State personnel. These estimates were based upon their impressions of the test plot results previously discussed

Table 8—Estimated decrease in production and value of pears due to pear psylla damage in 1977, test plot data, generalized to pear industry, Oregon, Washington, and California

Area & pear variety	Average production a/	Decrease in 1977 due to pear psylla damage b/		Loss due to change in		Total loss
		Production	Value per ton c/	Production	Value c/	
	tons		dollars			
OREGON	184,000	0	NA	0	932,600	932,600
Bartlett	77,667				238,600	238,600
Winter	106,333	0	NA	0	694,600	694,600
Hood River	104,017	0	0	0	0	0
Bartlett	43,217	0	0	0	0	0
Winter	60,800	0	0	0	0	0
Medford	79,983	0	NA	0	932,600	932,600
Bartlett	34,450	0	NA	0	238,000	238,000
Fresh	6,952	0	34.32	0	238,000	238,000
Processed	27,498	0	0	0	0	0
Winter	45,533	0	15.25	0	694,600	694,600
WASHINGTON	223,100	11,484	NA	1,476,600	1,318,300	2,795,100
Bartlett	133,300	10,631	NA	1,348,800	783,200	2,132,000
Fresh	41,560	3,321	20.48	388,600 d/	783,200	1,171,800
Processed	91,740	7,330	0	960,200 e/	0	960,200
Winter	89,800	835	6.02	127,800 f/	535,300	663,100
CALIFORNIA	323,916	0	0	0	0	0
Bartlett	316,333	0	0	0	0	0
Winter	9,383	0	0	0	0	0
TOTAL	733,016	11,484	NA	1,476,600	2,251,700	3,728,300
Bartlett	527,300	10,631	NA	1,348,800	1,021,800	2,370,600
Winter	205,716	835	NA	127,800	1,229,900	1,357,700

a/ Taken from table 1 of USDA/State Assessment Team Report, 1978;

b/ Based on test plot data supplied by Agricultural Extension Service personnel in respective areas.

c/ Estimated change in weighted average value due to pears being downgraded because of pear psylla damage.

d/ Decrease in marketable pears (increase in cull pears) due to pear psylla damage times 1974-76 weighted average value per ton of fancy pears.

e/ Decrease in marketable pears (increase in cull pears) due to pear psylla damage times 1974-76 weighted average value per ton of canning pears.

f/ Nonmarketable production due to pear psylla damage times 1974-76 weighted average value per ton.

SOURCE: USDA State Assessment Team, 1978.

and on their professional experience with pesticides and pear psylla.

The agricultural specialists in each pear-growing region made two significant assumptions about the potential losses for 1978-81: first, without amitraz, overall fruit quality would decline progressively each year and second, trees would continuously be lost. These assumptions were translated into estimated rates of losses which are listed in Table 9.

Table 9. Estimated Rates of Losses Due to Pear Psylla If Amitraz Is Unavailable in 1978-1981.

Region	Variety	Estimated Tree Loss Due to Pear Decline	Estimated Fruit Quality Losses
Medford, OR	Bartlett	1.5% per year	10% per year
	Winter	1.5% per year	10% per year
Hood River OR	Bartlett	0 in 1978	2% in 1978
		5% over 1979-81	4% over 1979-81
	Winter	0 in 1978	10% in 1978
		10% over 1979-81	15% over 1979-81
Wenatchee WA	Bartlett	0	13% in 1978
			8% per year for 1979-81
	Winter	0	15% in 1978
			8% per year for 1979-81
Hopeland CA	Bartlett	2% per year	5% per year
	Winter	2% per year	5% per year

Table 10 presents estimated decreases in returns in 1978-81 for both production and value. Losses due to decreased production include losses due to increased culls and to weakened and dead trees. Losses due to decreases in value would be incurred because of the lower price received for pears downgraded because of psylla damage.

To evaluate these expected revenue losses, each year's loss was expressed in terms of value as of a base year. This was done by discounting the estimated future revenue losses and reduced spray costs without amitraz back to a present value for 1977, using a rate of 7% a year.

Projected reductions in the total value of pears, discounted to 1977 dollars, were estimated at $6.2 million,

Table 10 Estimated decrease in value of pears due to pear psylla damage if an effective summer control such as amitraz is unavailable in 1978, 1979, 1980, and 1981, Oregon, Washington, and California[a]

Area and pear variety	1976-78[b] Average value	1978[c] Loss due to change in Production	1978[c] Loss due to change in Value	1978[c] Total loss	1979[c] Loss due to change in Production	1979[c] Loss due to change in Value	1979[c] Total loss	1980[c] Loss due to change in Production	1980[c] Loss due to change in value	1980[c] Total loss	1981[c] Loss due to change in Production	1981[c] Loss due to change in Value	1981[c] Total loss
	thousand dollars												
OREGON	25,797	169	2,338	2,506	1,499	3,250	4,748	1,667	3,547	5,214	1,835	3,600	5,436
Winter	15,322	99	1,622	1,721	1,068	1,982	3,050	1,166	2,036	3,203	1,265	2,087	3,353
Hood River	14,328	0	986	986	1,161	1,395	2,556	1,161	1,396	2,557	1,161	1,395	2,556
Bartlett	5,834	0	117	117	292	222	513	292	222	514	292	222	513
Winter	8,494	0	869	869	869	1,174	2,043	869	1,174	2,043	869	1,173	2,043
Medford	11,233	169	1,352	1,521	337	1,758	2,096	506	2,151	2,657	674	2,531	3,205
Bartlett	4,631	70	599	669	139	950	1,089	209	1,289	1,498	278	1,617	1,895
Fresh	1,173	18	258	276	35	278	313	53	296	349	70	314	384
Proc.	3,463	52	341	393	104	672	776	156	993	1,149	208	1,303	1,511
Winter	6,602	99	753	852	198	808	1,006	297	862	1,159	396	914	1,310
WASHINGTON	32,134	2,624	337	2,962	2,835	364	3,199	3,061	393	3,454	3,306	425	3,731
Bartlett	10,393	1,319	170	1,490	1,425	184	1,609	1,539	199	1,738	1,662	215	1,877
Fresh		358	170	528	387	184	571	417	199	616	451	215	666
Proc.		961	0	961	1,038	0	1,038	1,121	0	1,121	1,211	0	1,211
Winter	21,739	1,305	167	1,472	1,410	180	1,590	1,522	194	1,717	1,644	210	1,854
CALIFORNIA	48,034	336	823	1,159	672	1,614	2,286	1,009	2,371	3,380	1,345	3,094	4,439
Bartlett	46,501	325	797	1,122	651	1,562	2,213	977	2,295	3,272	1,302	2,995	4,297
Winter	1,533	11	26	37	21	52	73	32	76	108	43	99	142
TOTAL	105,985	3,129	3,498	6,627	5,005	5,228	10,233	5,737	6,310	12,047	6,486	7,445	13,931
Bartlett	75,381	1,714	1,683	3,397	2,507	3,014	5,521	3,016	4,004	7,020	3,534	5,048	8,582
Winter	30,384	1,415	1,815	3,230	2,498	2,214	4,712	2,721	2,306	5,027	2,952	2,397	5,349

a/ Data may not add due to rounding.

b/ Taken from table 1.

c/ Detailed calculations used in estimating losses are presented in Appendix III of USDA/State Assessment Team, 1978.

Source: USDA State Assessment Team, 1978.

b. Consumers

Psylla damage to pears is called russet. Russet impedes uniform ripening, resulting in hard green spots under the russet areas after the rest of the fruit has ripened. These spots decrease the value of the pears in the fresh fruit market because the price consumers are willing to pay is largely based on appearance. In addition, the blades of automatic peelers become caught in the russet areas and tear out chunks of the flesh, thereby damaging the halves; these halves are either packed as imperfects or cut up for fruit cocktail. Thus, pear psylla russet also decreases the value of processed pears. In either case, the return to the grower is substantially reduced.

Without amitraz, the quantity of pears in the market may be decreased if there is an increase in culls and if there is a loss of productive trees. Pear psylla damage without amitraz is projected to reduce the quantities of pears in the market during 1977, 1978, 1979, 1980 and 1981 by 1.6%, 2.9%, 4.5%, 5.0% and 5.5%, respectively (these figures do not take into account the possible replacement of pear acreage with more profitable crops). These reductions in quantity would lead to somewhat higher retail prices. The full effect on price would ultimately depend on consumer acceptance of a lower quality U.S. Grade #2 pear.

C. Qualitative Assessment of Benefit Data

In determining whether or not the benefits of a pesticide outweigh the risks associated with its use, the Agency must consider not only the magnitude of the estimated benefits, but also the quality of the benefits data and the extent to which estimates of economic impact are supported by an empirical data base.

1. Apples

The Agency believes that there was an adequate data base for the USDA/State Assessment Team to evaluate the potential use of amitraz on apples. Nine field trials conducted in 1976 and 1977 on apple orchards provided an extensive data base for comparing the efficacy of amitraz to other registered miticides (Entomological Society of America 1977, 1978). These test plots involved several varieties of apples, several states, different formulations of products, most of the registered apple miticides and all of the pest species listed on the proposed BAAM label. Although the test results varied, the data indicated that amitraz and the alternative registered miticides provide comparable levels of mite control. Because of these findings, it was concluded by the Assessment Team that no overall change in apple yield or quality would result from the introduction of amitraz.

$8.9 million, $9.8 million and $10.6 million at the end of the first, second, third and fourth years, respectively. Column 3 of Table 11 presents the impacts on net present income to growers, taking into account lower costs of alternative spray programs.

Table 11: Projected Reductions in Pear Value Due to Unavailability of Amitraz during 1978-1981

Year	Reduced grower revenue discounted to 1977	Decrease in control costs without amitraz discounted to 1977	Total impact discounted to 1977
1978	$ 6,193,000	$ 692,000	$ 5,501,000
1979	$ 8,938,000	$ 647,000	$ 8,291,000
1980	$ 9,834,000	$ 605,000	$ 9,229,000
1981	$10,628,000	$ 565,000	$10,063,000

Reduction in the quantities of marketed U.S. Grade #1 pears, increases in culls, and lower overall production of pears, of the magnitude projected in this analysis, would lead to overall revenue gains for pear growers not affected by pear psylla. This would offset, to some degree, the user impacts from reduced quality and production on the acreage currently needing amitraz. Also, the affected pear orchards would eventually be uprooted and planted with more profitable crops.

As stated earlier, the efficacy of amitraz for summer control of pear psylla was assumed to be similar to that of chlordimeform; therefore, the average gross return per acre from 1974-76, when chlordimeform was in use, was considered to be the per acre return which could be expected from the use of amitraz. Based upon this assumption, the average gross per acre return for pears treated with amitraz is estimated to be $1,368. Direct costs of production and annual land, fixed capital and management costs are $1,038 per acre. Therefore, the average returns to land, fixed capital and management is $330 per acre.

In the long term, returns to land, fixed capital and management determine if pear growers can continue to produce pears. Based on estimates of returns to land, fixed capital and management during an untreated period of 5 years, by the end of the fifth year, per acre returns would be reduced from $330 to $89. If such reductions actually occurred, the affected growers could ultimately be forced out of business.

The Agency concurs with the Team's conclusion that amitraz would not perform significantly better than other registered miticides, that amitraz would have a negative economic impact, and that the only potential benefit from amitraz would be in areas which might face mite resistance.

2. Pears

For pears, the data base was very small. Four test plots in different locations were set up to compare amitraz to the alternative spray programs. The results were variable, some showing no effect by either amitraz or the alternate spray program, some showing that amitraz was less effective than the alternate program and some indicating that it was more effective. Only a few of the available alternative insecticides were tested. The agricultural specialists pointed out that psylla infestation levels were lower than usual that year. They labeled two of the plots "atypical" because of this problem, because they thought the data from these two test plots may not be representative of all acres in the Northwest.

With the two remaining plots (Wenatachee, WA and Medford, OR), the economists assumed that the better performance by amitraz would be repeated on all the affected acres in Oregon, Washington and California. They then used the data from these two plots to extrapolate 1977 impacts for the entire Pacific Northwestern pear production area. Thus, the figures obtained were essentially based on the opinion of the agricultural specialists and not entirely upon experimental test plots or other documented field evidence.

To estimate economic impacts of the unavailability of amitraz for 1978-1981, the economists obtained from Assessment Team members estimates of losses due to pear tree decline and pear quality grading decreases. There were no empirical data cited in the analysis provided to the Agency supporting the occurrence of pear decline or quality losses due to pear psylla. In addition, anomalies in the benefits estimates have undermined the reliability of these estimates.

The only adequate empirical data made available to the Agency were test plot data demonstrating that amitraz is as efficacious as chlordimeform (Luttner 1976).

Thus, the Agency considers the data base for the economic estimates of the benefits of amitraz to be very weak. The Agency has concluded that the use of four test plots as data bases for the entire Pacific Northwest pear production area would not produce a reliable extrapolation of potential losses in 1977. Furthermore, it has been concluded that the projection of losses for the 1979-1981 period could not be reliably achieved solely on the basis of expert opinion, because of the absence of an empirical data base.

The Agency concludes, despite the deficiencies mentioned above, that the adverse economic impact on pear growers and consumers may be substantial in the short-term if amitraz is not available. However, the Agency does not consider the data base adequate to estimate the long-term economic effects of continued unavailability of amitraz.

IV. Development and Selection of Regulatory Option

This section of the Position Document discusses the basis for the Agency's development of regulatory options, evaluates methods of risk reduction, and then identifies the four options selected for consideration.

A. Basis for the Development of Options

As explained in Part I, the Administrator may register a pesticide only if he has first determined that its use will not pose an unreasonable risk to man or the environment. This determination must be made for each proposed use of a pesticide and must take into account the risks and benefits associated with each use. Even if the Administrator determines that a pesticide will pose an unreasonable risk if used as proposed, before denying registration he must consider whether prescribing any restrictions on the pesticide's use or user will sufficiently reduce the risks to warrant registration.

It is therefore apparent that the Administrator must consider a spectrum of regulatory options for each use of a pesticide. Approval of registration with no added restriction and denial of registration are absolute regulatory options at opposite ends of this spectrum. In between these absolutes, the Administrator may consider options which approve registration but with prescribed restrictions and conditions designed to reduce risks. For example, the Administrator may specify the permissible sites for use, directions for use, and label and labeling language and may require that the pesticide be used by certified applicators only.

Under special circumstances, the Administrator may conditionally register a pesticide for a limited period of time. The conditional registration provision of FIFRA which is applicable to amitraz is Section 3(c)(7)(C) of FIFRA as amended in 1978. This section provides that the Administrator may conditionally register a pesticide not currently registered if he determines: first, a period reasonably sufficient for the generation and submission of data required for unconditional registration has not elapsed since the Administrator first imposed the data requirement; second, use of the pesticide during the period of conditional registration will not cause any unreasonable adverse effects; and third, use of the pesticide is in the public interest. If the Administrator makes these determinations and grants conditional registration, such registration shall be subject to the conditions that, first, the data submission requirement be satisfied before the specified term of the registration has expired and, second, the newly submitted data not meet or exceed any of the risk criteria enumerated in 40 CFR 162.11. In addition, the Administrator may prescribe any other condition he deems appropriate. If the Administrator determines that the registrant has failed to take appropriate steps toward fulfilling any condition imposed or that a condition has not been met within the period prescribed for satisfying such condition, he shall issue a notice of intent to cancel the conditional registration.

Amitraz falls within the purview of Section 3(c)(7)(C), because it is not currently registered for use as a pesticide. Although technical amitraz is registered, this registration is for formulation only, not for pest control. The Agency considers the provisions of Section 3(c)(7)(C) to apply to pesticides which are not currently registered for an end use.

Before developing the regulatory options for amitraz, the Agency has first considered a wide range of conditions of registration for amitraz: classification of amitraz for restricted use, (i.e., for use only by certified applicators); preharvest intervals; protective clothing; respirators; reentry intervals; and additional data for registration. In the following section, the Agency has assessed the extent to which these conditions would reduce risk, are feasible, and are otherwise desirable.

B. Conditions of Registration Considered

1. Classification For Restricted Use

Under FIFRA, hazardous pesticides may be classified for restricted use and be limited to use only by or under the direct supervision of certified applicators. Certification programs are administered primarily by the States. These programs use various methods to certify applicators, after a determination that these applicators are competent to use restricted pesticides.

The Agency believes that the classification of amitraz for restricted use would ensure that the material would be available only to competent persons. Preventing untrained persons from using amitraz would significantly reduce the risk of human exposure due to misuse or carelessness. Any marginal costs that might result from restriction to certified applicators would be minimal, since state programs to certify applicators are operational in all states, since there are many certified applicators, and since there is little difficulty in obtaining applicator certification.

2. Preharvest Intervals (PHI)

Residues of amitraz may be expected to occur in the two food crops, apples and pears, for which amitraz is currently being considered for registration. These residues would arise from amitraz deposition on fruit.

The Agency has explored the possibility of reducing these residues by controlling the time of application. Specifically, the residues could be reduced if the preharvest interval (PHI), the time lapse between application and harvest, were lengthened. This would allow the residues of amitraz on or in the fruit to partially dissipate before the fruit is harvested and marketed.

After reviewing pear residue data collected by the Upjohn Company between 1974 and 1976, the Agency has determined that increasing the PHI from 1 day to 7 days will reduce the average amitraz residues in pears by about 20% (1.15 ppm for 1 day PHI versus 0.88 ppm for 7 day PHI) (Beusch 1978). Furthermore, upon comparison of Upjohn's mean value of 1.0 ppm for a 1 day PHI (Appendix 1) to the mean values of 0.42-0.52 ppm for a 7 day PHI obtained from the Upjohn-APHIS study (Appendix 2), it appears that the residues might be reduced by as much as 50%. The Agency has also found that the 7-day PHI is economically feasible and practical for growers (Luttner 1978).

For apples, the Agency has discovered that to lengthen the proposed PHI of 14 days to 30 days would not create major problems for most growers, but would pose a problem for certain early-maturing apple varieties, such as McIntosh.

3. Protective Clothing

Dermal exposure to amitraz is of considerable concern to the Agency; this exposure may arise from any of several application operations:

a. mixing and loading, spills, maintenance of application equipment,

b. ground spray application, and

c. aerial spray application (including wind drift).

Mixing, transfer and cleanup of spills pose a significant risk of dermal exposure to the concentrated material. Protection of the body requires wearing a long-sleeve shirt (fine weave), long pants (fine weave), rubber gloves, an apron and boots.

Significant dermal exposure to amitraz is also incurred during ground spray application. Amitraz is normally applied with an airblast sprayer. The amount of amitraz that could be absorbed through the skin could be as high as 1.26 to 1.53 mg/kg/day amitraz. Protective clothing, including gloves, boots, long-sleeve shirt (fine weave), and long pants (fine weave), would reduce the risk of dermal exposure by a factor of about five (Garner 1978b).

During aerial application of amitraz, dermal exposure to the pilot is two orders of magnitude less than that for a ground spray operator (Garner, 1978a). Therefore, the Agency did not consider requiring protective equipment for pilots.

4. Respirators

Respiratory exposure to amitraz will occur during mixing, loading and application of the pesticide (see Table 3). However, because it is about four orders of magnitude below the dermal exposure for applicators, the Agency did not consider requiring respirators.

5. Reentry Intervals

Dermal and inhalation exposure to amitraz might arise for farm workers from dislodgable residues immediately following application of the pesticide. Prohibiting reentry until the leaves are completely dry and at least until 24 hours after application would eliminate the risk incurred by farm workers from any potential dislodgable residues.

6. Conditional Registration for a Period of 4 Years with the Requirement That Additional Risk and Benefit Data Be Submitted within That Period

If the Agency concludes that the data required for unconditional registration has not yet been generated and that the prerequisites for conditional registration under Section 3(c)(7)(C) of FIFRA have been met, then the Agency may consider conditionally registering amitraz for a period of 4 (four) years, the time estimated to be necessary for the generation and submission of the required data. If such registration were granted the Agency would require that another mouse oncogenic study be performed within 4 years. The Agency would also require that the registrant submit test data adequate to substantiate the estimated benefits of amitraz. Such data would be submitted to EPA within 4 years and in annual progress reports. The kind of data which would be requested by the Agency would generally consist of: first, data which clearly demonstrate the comparative performance of amitraz as compared to all other pesticides currently registered for pear psylla, as measured by the numbers of adult and nymph pear psylla killed, yield, and russet damage and other quality measurements; second, data which indicate the rate of tree deterioration due to pear decline that results from the use of the presently registered alternatives as compared to amitraz; and third, estimated economic short and long-term impacts based on the results of this empirical test data. The protocols, results and dates of submission would be specified in the notice of conditional registration.

Risks to applicators and to the public resulting from the use of amitraz for 4 years would be much less than if amitraz were unconditionally registered and used for an indefinite period of time. Specifically, the risks to applicators posed by conditional registration would be 4/40 or 10% of the risk posed by full registration, since the applicators would be exposed 4 years rather than 40 years. Similarly, individuals consuming treated fruit would have 4/70, or 6% of the risks associated with full registration, because they would be exposed 4 years instead of 70 years.

C. Regulatory Options Selected

From the range of possible restrictions and conditions for registration, the Agency has formulated four regulatory options for the ultimate registration decision. In Part V, these options will be considered and evaluated for each use of amitraz. In order of increasing restrictiveness, the options selected are:

Option 1. Register amitraz as proposed by the registrant.

If this option is chosen, amitraz would be classified for general use on pears and apples. Registration of amitraz would establish a pre-harvest interval of 1 day for pears and 14 days for apples. The registration of amitraz would also require the establishment of tolerances of 1 ppm in or on pears and 3 ppm in or on apples.

Option 2. Register amitraz with additional use restrictions.

The choice of this option would restrict the use of amitraz to certified applicators, would require the wearing of protective clothing during mixing and loading and ground spray application, and would establish a 7 day PHI for pears and a 14 day PHI for apples. During mixing and loading, protective clothing would include a longsleeve shirt (fine weave), long pants (fine weave), rubber gloves, boots, and an apron. For ground spray application, protective clothing would include gloves, boots, longsleeve shirt (fine weave) and long pants (fine weave).

Option 3. Condititionally register amitraz for 4 years; require submission of additional risk and benefit data; and prescribe same use restrictions as in Option 2.

If amitraz were conditionally registered, the sale and use of amitraz would be permitted for only 4 years, unless unconditional registration were eventually granted. In addition, the applicant for registration would be required to submit another mouse oncogenic bioassay as well as the benefits data (see Part III.B.) within 4 years with annual reports of progress and test results. Amitraz would be subject to the same use restrictions as prescribed in Option 2.

Option 4: Deny the registration of amitraz.

This option would be chosen if the Agency concludes that the risks of amitraz outweigh benefits during a conditional or full registration*/.

V. Review of the Impacts of the Major Options

This section evaluates on a use-by-use basis the overall risks and benefits of each regulatory option developed in Part IV. All information necessary for this evaluation has been described in Parts II and III. Tables 12 and 13 summarize the impacts of the regulatory options on human health, the environment, growers and consumers.

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*/ Even if the Agency denies the registration of amitraz, it may still consider applications from states for emergency exemptions from FIFRA. 40 CFR 166.1 provides that such exemptions may be granted only if: (a) a pest outbreak has or is about to occur and no registered pesticide or alternative method of control is available to eradicate or control the pest, (b) significant economic or health problems will occur without the use of the pesticide, and (c) the time available from discovery or prediction of the pest outbreak is insufficient for a pesticide to be registered for the particular use. In determining whether an emergency condition exists, the Administrator will also give consideration to additional facts presented by the applicant.

An exemption, if granted, is valid only for the specific situation involved and is subject to such restrictions as the Administrator may prescribe. These restrictions may include, among others, limitation on the quantity of the pesticide to be used, the conditions under which the pesticide may be applied, restrictions as to the persons who may apply the pesticide and the type of monitoring activities which should be conducted. Specific exemptions, if granted, are valid only for the time specified, but under no circumstances shall be longer than 1 year.

Table 12. Impacts of Regulatory Options for Amitraz on Apples

REGULATORY ALTERNATIVES	AMITRAZ RISKS TO HUMANS ROUTES OF EXPOSURE	 RISKS	RISKS FROM SUBSTITUTES ENVIRONMENTAL HUMAN	ECONOMIC IMPACTS GROWERS	 CONSUMERS	DISCUSSION OF ISSUES AND TRADE-OFFS
1. Register amitraz.	Oral ingestion of food residues by U.S. population Dermal and inhalation exposure for applicators.	8 cancer cases/yr in U.S. from eating treated apples and cases/yr for exposed applicators.	Two registered substitutes cyhexatin and propargite are more toxic to fish and wildlife substitutes.	Cyhexatin and propargite are efficacious and cost less than amitraz.	Present prices continue.	Risks occur for U.S. population and applicators.
2. Register amitraz with Additional Use Restrictions and Data Requirements	Risks are reduced by about a factor of 5 for applicators. (i.e., 0.0004 cancer cases/yr). No reduction for U.S. population eating treated fruit.			"	"	Grower compliance is likely.
3. Conditionally Register amitraz for 4 years.		Risks are 4/70 of Option 2 for persons eating apples (0.5 cancer case/yr) and 4/40 for applicators (0.00004 cancer case/yr)	"	"	"	The Agency would approve or disapprove full registration at the end of 4 yrs.
4. Deny Registration.		Amitraz risks would be eliminated unless an emergency exemption were granted. Such exemptions are unlikely due to availability of substitute pesticides.	"	"	"	Some growers might someday have a problem with mite resistance to other chemicals.

Table 13. Impacts of Regulatory Options for Amitraz on Pears

REGULATORY ALTERNATIVES	AMITRAZ RISKS TO HUMANS		RISKS FROM SUBSTITUTES		ECONOMIC IMPACTS		DISCUSSION OF ISSUES AND TRADE-OFFS
	ROUTES OF EXPOSURE	RISKS	ENVIRONMENTAL	HUMAN	GROWERS	CONSUMERS	
1. Register amitraz.	Oral ingestion of food residues by U.S. population Dermal and inhala- by U.S. population Dermal and inhalation exposure for applicators.	Oncogenicity: 6 cancer cases/yr from eating cancers cases/yr from eating treated fruit and 0.004 cancer cases/yr. for exposed applicators.	Two of substitutes (mancozeb, zineb) are under RPAR review. Two other are under RPAR review. Two other substitutes (oil, endosulfan) present no hazards.		Production and quality maintained at 1974-1976 levels (when chlordimeform was available).	Present prices continue.	Risks occur for U.S. population and applicators.
2. Register amitraz with Additional Use Restrictions and Data Requirements.	Risks are reduced by about a factor of 5 for applicators and (i.e, 0.0008 cancers/yr) and by 25% for U.S. population eating treated fruit (i.e., 15 cancer cases/yr).		"		"	"	Grower compliance is likely.
3. Conditionally Register amitraz for 4 years.	Risks are 4/70 of Option 2 for persons eating pears (0.08 cancer cases/yr) and 4/40 of Option for applicators 0.00008 cancer cases/yr).		"		"	"	The Agency would approve or disapprove full registration at the end of 4 years

.057
7.1 4.00
35
50

.067
8
.456

Table 13. Impacts of Regulatory Options for Amitraz on Pears

REGULATORY ALTERNATIVES	AMITRAZ RISKS TO HUMANS		RISKS FROM SUBSTITUTES		ECONOMIC IMPACTS		DISCUSSION OF ISSUES AND TRADE-OFFS
	ROUTES OF EXPOSURE	RISKS	ENVIRONMENTAL	HUMAN	GROWERS	CONSUMERS	
4. Deny Registration..		Amitraz risks would be eliminated unless an emergency exemption were granted. Such exemptions are likely as long as no substitute pesticide is available. However, fewer acres would be treated than under Options 1, 2, or 3.		*	Grower and consumer impacts could be as high as those listed below. But granting Section 18's would greatly reduce or eliminate those impacts by allowing BAAM to be used only were absolutely needed.		Several states will continue to apply for emergency exemptions.
					Net Losses: 1978 = $ 6,193,000 1979 = $ 8,291,000 1980 = $ 9,229,000 1981 = $10,063,000 4 yrs =$33,084,000	Unquantified, but significant increase in retail prices possible.	
					Grower returns reduced from $330/A to $276/A the first year; to $89/A after 5 yrs. Many pear orchards might be uprooted as a result.		

A. Apples

Option 1: Register amitraz as proposed by the registrant.

Choosing Option 1 would indicate the Agency's conclusion that the risks of using amitraz as proposed by the registrant on apples are outweighed by the benefits of such use and, therefore, that no unreasonable adverse effects would result.

This option would result in a hypothetical risk of 6 cancers cases/year (or 2×10^{-6} lifetime risk per person) for the U.S. population consuming treated apples, 0.002 (or 1×10^{-4} lifetime risk per person) cancers cases/year for ground spray applicators, and less than 0.0001 zero cancers cases/year (3×10^{-6} lifetime risk) for helicopter applicators. Option 1 is not expected to result in any greater hazard to birds, fish and other wildlife than the use of the substitute pesticides.

There would be a negative economic impact for growers who might use amitraz, since it costs more than other registered pesticides which are equally efficacious. If all of the 52,000 acres with a mite problem were treated with amitraz, the increased control cost would be $410,000, or $7.89 per acre. For a grower with an average size orchard of 32 acres, the impact would be 32 X $7.89 = $253.00 per year in higher control costs due to amitraz. The only potential benefit of registering amitraz for apples would be to make an additional material available to rotate with existing miticides to minimize the possibility of mite resistance.

Option 1 would have no effect on consumer prices.

Option 2: Register amitraz with additional use restrictions

Choosing this option would indicate the Agency's conclusion that the benefits from using amitraz on apples outweigh the risks and will not result in unreasonable adverse effects, provided that additional restrictions are placed on the terms and conditions of the registration.

This option would not reduce the hypothetical cancer risks to the U.S. population through ingestion of treated apples, but would decrease the exposure and risks to ground applicators and mixers and loaders by about a factor of five. Option 2 is not expected to result in any greater hazard to birds, fish and other wildlife than the use of the substitute pesticides.

The negative economic impact for growers under Option 2 would be the greater than for Option 1 by about $25, the cost of protective equipment.

There would be no impact on consumer prices.

Option 3: Conditionally register amitraz for 4 years; require submission of risk and benefit data; and prescribe the same use restrictions as in Option 2.

Choosing this option would indicate the Agency's conclusion that the basic prerequisites for conditional registration under Section 3(c)(7)(C) have been met. Specifically, this choice would reflect the following Agency determinations: first, additional data are needed before the Agency can determine with adequate certainty whether the benefits of unconditional registration of amitraz for use on apples outweigh the risks of such registration; second, a sufficient period of time has not elapsed since the applicant was informed by the Agency or had reason to believe that generation of additional data would be required; third, no unreasonable adverse effects on man or the environment will occur as a result of the restricted use of amitraz on apples during the 4 year registration period; and fourth, a conditional registration is in the public interest.

The hypothetical risks to persons eating treated apples would be 4/70 that of Option 2 (i.e., 0.5 cancer cases/yr and 3×10^{-8} lifetime risk per person); to applicators the risks would be about 4/40 of Option 2 (i.e., 0.00014 cancer cases/yr and 1×10^{-6} lifetime risk per person).

As in Option 2, Option 3 is not expected to result in any greater hazard to birds, fish and other wildlife than the use of the substitute pesticides.

For growers, there would be the same negative economic impacts from using amitraz and from buying protective equipment as in Option 2. No impacts on consumer prices are expected.

Option 4: Deny registration of amitraz

Choosing this option would indicate the Agency's conclusion that an unconditional registration of amitraz on apples would result in unreasonable adverse effects, even if the additional restrictions of Option 2 were prescribed. It would also indicate the Administrator had concluded that conditional registration should not be granted either because unreasonable risks would result or because one of the other prerequisites for such registration had not been met.

All risks from the use of amitraz on apples would be eliminated, and the negative economic impacts on growers seen in Options 1, 2 and 3 would be avoided. Even so, a potential negative effect would be the unavailability of amitraz to rotate with other miticides to minimize the development of mite resistance to pesticides. There would be no effects on consumer prices.

In addition, the use of alternative registered miticides would continue without any apparent unreasonable adverse effects on humans or the environment. Although some of these alternatives are more toxic to fish, birds and estuarine species, it is not known whether exposure to these organisms occurs. The label precautions are designed to minimize such exposures.

B. Pears

Option 1: Register amitraz as proposed by the registrant

Selecting Option 1 for pears would indicate the Agency's conclusion that the risks of using amitraz as proposed on pears are outweighed by the benefits of such use; therefore, no unreasonable adverse effects would result.

This option would result in a hypothetical risk of 8 cancer cases/year (2×10^{-6} lifetime risk per person) to the U.S. population consuming treated pears, of 0.04 cancer cases/ year (1×10^{-4} lifetime risk per person) to ground-spray applicators, and of less than 0.00001 cancer case/year to helicopter applicators. Option 1 is not expected to result in any greater hazard to birds, fish and other wildlife than the use of the substitute pesticides.

On the benefit side, this option would prevent a roughly approximated maximum loss of $33,000,000 to affected growers during 1978-1981. Consumer price increases, which could result if amitraz were unavailable, would also be avoided.

Option 2: Register amitraz with additional restrictions

Selecting Option 2 would indicate the Agency's conclusion that the benefits from using amitraz as proposed on pears outweigh the risks and thereby do not result in unreasonable adverse effects, provided that additional restrictions are placed on the terms and conditions of registration.

This option is anticipated to reduce the hypothetical cancer risks to the U.S. population by about 20% to 50%. The risks to applicators would be reduced by about a factor of 5. Option 2 is not expected to result in any greater hazard to birds, fish and other wildlife than the use of the substitute pesticides.

A roughly approximated maximum loss of $33,000,000 to growers during 1978-1981 would be prevented; however, the requirement for protective equipment would cost growers about $25 each. Consumer price increases, which could result if amitraz were unavailable, would also be avoided.

Option 3: Conditionally register amitraz for 4 years; require submission of additional risk and benefit data; and prescribe the same use restrictions as in Option 2.

Choosing this option would indicate the Agency's conclusion that the basic prerequisites for conditional registration under Section 3(c)(7)(C) have been met. Specifically, this choice would reflect the following Agency determinations: first, additional data is needed before the Agency can determine with adequate certainty whether the benefits of unconditional registration of amitraz for use on pears outweigh the risks of such registration; second, a sufficient period of time has not elapsed since the applicant was informed by the Agency or had reason to believe that generation of additional data would be required; third, no unreasonable adverse effects on man or the environment will occur as a result of the restricted use of Amitraz on pears during the 4 year registration period; and fourth, a conditional registration is in the public interest.

The hypothetical risks for persons eating treated pears would be 4/70 that of Option 2 (i.e., 0.08 cancer case/yr; or 3×10^{-8} lifetime risk per person). For applicators the risks would be 4/40 of Option (i.e.) 0.00008 cancer cases/yr; or 1×10^{-6} lifetime risk per person). Option 3 is not expected to result in any greater hazard to birds, fish and other wildlife than the use of the substitute pesticides.

For growers, a maximum loss roughly approximated to be $33,000,000 during 1978-1981, would be prevented, although the requirement for protective equipment would cost growers about $25 each. Consumer price increases would also be avoided.

Option 4: Deny registration of amitraz

Selecting this option would indicate the Agency's conclusion that unconditional registration of amitraz on pears would result in unreasonable adverse effects, even if the additional restrictions of Option 2 were prescribed. It would also indicate that the Administrator had concluded that conditional registration (Option 3) should not be granted because unreasonable risks would result or because one of the other prerequisites for such registration had not been met.

This option would eliminate all risks from amitraz use on pears, but may have a maximum adverse impact of $33,000,000 per year on growers, and may increase consumer prices.

The uses of the major alternative registered miticides (mancozeb, zineb, oil and endosulfan) would continue. The first two of these chemicals are under RPAR review for potential unreasonable adverse effects on man, including oncogenicity, mutagenicity and teratogenicity. From available data, the last two compounds, oil and endosulfan, are not anticipated to have unreasonable adverse effects on man or the environment. However, there are significant data gaps for these two alternatives.

VI. Recommended Regulatory Actions

To determine the appropriate regulatory actions for amitraz, the Agency must decide which of the possible options achieves the most appropriate balance between risks and benefits. In this section, the Agency has compared the risks and benefits of the regulatory options for each use. Then the Agency has listed for each use the options which it has rejected and the reasons for rejection. Finally, the recommended options are described as well as the rationale for their selection.

A. Apples

1. Comparison and Analysis of Options Not Recommended

Option 1 (unconditional registration), Option 2 (restricted unconditional registration) and Option 3 (4 year conditional registration) might result in small potential cancer risks for applicators and the U.S. population. Although there are uncertainties which may undermine the reliability of the risk data (see Part II), the Agency concludes that the data is sufficient to determine that there is some risk. The Agency has also determined that there would be no significant economic benefits to offset these risks. In fact, since amitraz costs more than the available alternative miticides, use of the chemical would probably have negative economic impacts for growers.*/

2. Recommended Option

Option 4 is the most reasonable course of action, for apples, because: first, it would eliminate a small risk of cancer to humans; second, it would result in the continued use of substitutes which appear to be less hazardous to man than amitraz**/; and third, it would have no effect on the economics of apple production.

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*/ The availability of amitraz for rotation with alternative pesticides might help minimize mite resistance, but this benefit is speculative.

**/ Although most of the substitute pesticides are more toxic to wildlife than amitraz, the potential exposure and actual hazards to wildlife are unknown.

B. Pears

1. Comparison of Options

Option 1, registration of amitraz, and Option 4, denial of registration, represent opposite ends of the regulatory spectrum. Under Option 1, the Agency would allow the benefits of amitraz with small but unmitigated cancer risks. In contrast, Option 4 would eliminate all risks from amitraz, but may have significant adverse economic impacts on growers affected by pear psylla, and may also affect consumers through increased pear prices.

Options 2 and 3 offer intermediate solutions. Option 2 reduces the risks of Option 1 by about a factor of five (80%) for applicators and by 20% to 50% for the U.S. population; and Option 3 further reduces the risks under Option 2 to applicators and the U.S. population to 4/40 and 4/70, respectively, of the risks under Option 2. Option 2 offers the same benefits as Option 1 minus the cost of protective equipment, while Option 3 limits the benefits of Option 2 to a four year time period.

2. Analysis of Options Not Recommended

As discussed in the preceeding consideration of the use of amitraz on apples, the Agency has determined that the risk data are inadequate for predicting long-term risks, due to the uncertainties about those data. The Agency has also found that the benefits data for pears are not reliable enough for making long-term projections. Consequently, the Agency concludes that the risk and benefit data are not sufficiently reliable for determining whether or not the long-term impact of Option 1 (unconditional registration) or Option 2 (unconditional restricted registration) would constitute unreasonable adverse effects. Even if the data had been reliable, the Agency would have rejected Option 1 because the restrictions proposed under Option 2 would significantly reduce the risks to a very low cost in relation to the estimated benefits of the use of amitraz on pears.

Option 4, which would deny registration, has been rejected, because of all of the following reasons considered together. First, although the benefits information is inadequate to balance the long-term benefits and risks, the Agency concludes that substantial short-term economic losses may occur if use of amitraz is completely denied. Second, although the risk data are inadequate to balance the long-term benefits and risks, the Agency concludes that the data are sufficient to determine that the risks posed by use of amitraz for a short period of time (4 years) on pears are very small. Third, all the legal prerequisites for conditional registration under Option 3 have been met, including the determination that no unreasonable adverse effects would result.

3. Recommended Option

The Agency has determined that Option 3 is the most desirable course of action. It would allow conditional registration of amitraz for use on pears for 4 years. Label directions would specify that only certified applicators could spray amitraz, and would also require a 7 day preharvest interval, protective clothing requirements and a prohibition against reentry until the treated leaves are dry and in any event until 24 hours after application. This option would also require that additional benefits data and another mouse oncogenic bioassay be submitted within 4 years, with annual reports of progress and test results. If the registrant does not meet these stipulations, the conditional registration may be cancelled.

The following determinations are the reasons for recommending Option 3, and also indicate the Administrator's legal authority to grant conditional registration pursuant to Section 3(c)(7)(C) of FIFRA, as amended:

(1) Additional data are needed before the Agency can determine with adequate certainty whether the benefits of unconditional registration of amitraz on pears outweigh the risks of such registration. The inadequacy of the risk and benefit data for predicting long-term impacts has been discussed in Parts II and III.

(2) A sufficient period of time has not elapsed since the registrant was informed by the Agency or had reason to believe that generation of additional data would be required. The data requirements of Option 3 are considered "additional" data requirements, rather than "old" data requirements (i.e., those requirements which the applicant for registration had sufficient time to meet), for two reasons. First, the applicant asked the Agency about 2 years ago whether it should conduct another mouse oncogenic bioassay. The Agency advised the registrant not to do so until the Agency had evaluated the tissue slides from the first mouse study. This evaluation was just recently completed. Second, the registrant had no reason to believe that it would have to develop additional benefits data, because the Agency never requested such data from it.

(3) No unreasonable adverse effects on man or the environment are anticipated to occur as a result of the restricted use of amitraz on pears during the 4 year period of allowable use. The uncertainties associated with the risks and benefits data prevent the Agency from considering the long-term use of amitraz. In spite of these uncertainties, the Agency has determined that these data are sufficiently sound to conclude that a conditional registration of amitraz for use on pears for 4 years should pose only very small risks and should prevent economic losses that are likely to be substantial.

(4) Conditional registration is in the public interest. In addition to benefits to pear growers, Option 3 is anticipated to result in benefits to the general public. If use of amitraz is denied, a marked decrease in marketable pears is expected to result from pear tree destruction by pear psylla, increased proportions of cull (non-marketable) fruit, decreased tree production, and from replanting of pear acreage with more profitable crops. As a consequence, the use of amitraz appears to be necessary to meet consumer demand for pears. Furthermore, it is likely that reductions in the quantity of marketable pears would lead to somewhat higher retail prices for pears. On the basis of these consumer impacts and on the fact that there are very minute risks associated with Option 3, the Agency concludes that conditional registration of amitraz on pears is in the public interest.

In addition to these determinations, there is another reasons for recommending Option 3. The restrictions on use and the safety precautions prescribed in Option 3 are reasonable in that they would substantially reduce risks without impacting the benefits of the use of amitraz on pears. They are practical, likely to be followed and enforceable.

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Appendix 1. Amitraz Residues in Fruit Treated in 1974-1976 (reproduced from Boots-Upjohn rebuttal with permission of the Upjohn Company)

		Pears	
State	Residue (ppm)	Number of Cover Sprays	Treatment to Harvest Interval (days)
Calif.	0.78	3	1
Calif.	0.50	3	1
Calif.	0.52	3	1
Calif.	0.45	3	1
Mich.	0.50*	2	0
Mich.	0.78*	2	0
Mich.	1.18	2	0
Mich.	0.96	2	0
Mich.	0.89	3	1
Mich.	1.17	3	1
Mich.	1.19	3	1
Mich.	1.22	3	1
Mich.	1.20	3	1
N.Y.	1.69	5	1
Ore.	0.92	4	1
Ore.	1.28	4	1
Ore.	1.80	4	1
Ore.	2.75	4	1
Wah.	1.25*	3	1
Wash.	0.36*	3	1
Wash.	1.12	3	1
Wash.	0.99	3	1
Wash.	0.23*	4	1
Wash.	0.20*	4	1

* Values were calculated to the recommended maximum rate from values found at rates actually applied.

number of results = 24

mean = 1.00 ppm

standard deviation = 0.56 ppm

standard error of the mean = 0.12 ppm

95% confidence limits: 0.76-1.24 ppm

coefficient of variation = 56.5

Appendix 1. Continued

Apples

State	Residue (ppm)	Number of Cover Sprays	Treatment to Harvest Interval (days)
Mich.	1.02	3	14
Mich.	0.88	3	14
N.Y.	0.32	3	14
N.Y.	0.44	3	14
N.C.	0.25	3	14
N.C.	0.42	3	14
Calif.	0.77*	2	14
Calif.	0.90*	2	14
Calif.	1.33*	2	14
Calif.	1.88*	2	14
Wisc.	0.24	2	14
Wisc.	0.27	2	14
Mich.	0.55*	3	5
Mich.	0.73	3	5

* Values were calculated to the recommended rate from values found at rates actually applied.

number of results = 14

mean = 0.71 ppm

standard deviation = 0.47 ppm

standard error of the mean = 0.13 ppm

95% confidence limits: 0.44-0.99 ppm

coefficient of variation = 65.9

Appendix 2. Residues of Amitraz in Pears Treated in 1977 (Ford 1978)

Sample	ppm Amitraz per Sample		Lab Log No.
	Upjohn	NMRAL	
7 days after last treatment	0.91	0.63	800000
	0.71	0.56	800001
	1.10	0.81	800019
	1.51	1.16	800021
	0.93	0.73	800052
	0.40	0.36	800062
	0.73	0.64	800068
	0.52	0.54	800079
mean =	0.85 1/	0.67	
Harvested 12 days after last treatment	0.63	0.63	800004
	0.25	0.24	800012
	1.71	0.91	800023
	0.62	0.49	800025
mean =	0.80	0.57	
Ripen 7 days	0.97	0.65	800006
Pre-storage, wash & wax.	0.20	0.22	800014
	0.46	0.70	800053
	0.33	0.43	800063
	0.54	0.52	800069
mean =	0.38	0.47	
Stored 1 mo. and ripened	0.31	0.30	800016
	0.95	0.71	800031
	0.85	0.48	800033
	0.61	0.68	800054
	0.29	0.32	800064
	0.48	0.67	800070
	0.46	0.65	800086
mean =	0.66	0.63	

1/ Mean values calculated by EPA.

Stored 2 mo. and ripened	0.67	0.74	800035
	0.61	0.40	800037
	0.46	0.74	800055
	0.56	0.45	800065
	0.28	0.36	800071
	0.26	0.28	800073
mean =	0.47	0.49	
Stored 3 mo. and ripened	0.59	0.54	800039
	0.65	0.68	800041
	0.52	0.60	800056
	0.31	0.44	800066
	0.50	0.49	800072
	0.22	0.30	800075
	0.57	0.60	800089
mean =	0.44	0.51	800089
Stored 4 mo. and ripened	0.56	0.57	800043
	0.61	0.92	800045
mean =	0.59	0.75	
Stored 6 mo. and ripened	0.24	0.31	800077
	0.47	0.61	800081
	0.38	0.51	800092
	0.47	0.86	800094
mean =	0.21	0.27	
Post-Storage (Wash only)	0.83	0.71	800027
	0.54	0.46	
mean =	0.69	0.59	
Pre-canned	0.90	0.90	800058
Canned Pears	<0.05	0.08	800010
	0.05	0.10	800060
	<0.05	0.06	800095
mean =	<0.05	0.08	
nned pulp	2.2	1.21	800008
	0.84	2.24	800096
mean =	1.52	1.73	

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Stored 2 mo. and ripened	0.67	0.74	800035
	0.61	0.40	800037
	0.46	0.74	800055
	0.56	0.45	800065
	0.28	0.36	800071
	0.26	0.28	800073
mean =	0.47	0.49	
Stored 3 mo. and ripened	0.59	0.54	800039
	0.65	0.68	800041
	0.52	0.60	800056
	0.31	0.44	800066
	0.50	0.49	800072
	0.22	0.30	800075
	0.57	0.60	800089
mean =	0.44	0.51	800089
Stored 4 mo. and ripened	0.56	0.57	800043
	0.61	0.92	800045
mean =	0.59	0.75	
Stored 6 mo. and ripened	0.24	0.31	800077
	0.47	0.61	800081
	0.38	0.51	800092
	0.47	0.86	800094
mean =	0.21	0.27	
Post-Storage (Wash only)	0.83	0.71	800027
	0.54	0.46	
mean =	0.69	0.59	
Pre-canned	0.90	0.90	800058
Canned Pears	<0.05	0.08	800010
	0.05	0.10	800060
	<0.05	0.06	800095
mean =	<0.05	0.08	
nned pulp	2.2	1.21	800008
	0.84	2.24	800096
mean =	1.52	1.73	